

UNIVERSITY OF ALBERTA

Patterns of Referral for Breast Cancer

by

Mary Ellen Haggerty



A thesis submitted to the Faculty of Graduate Studies and Research in partial
fulfillment of the requirements for the degree of Master of Science

in

Medical Sciences - Public Health Sciences

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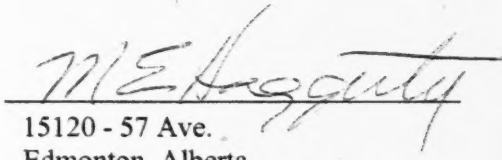
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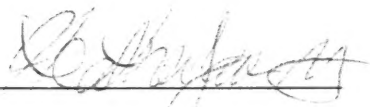
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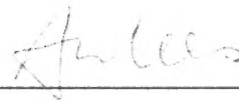
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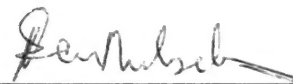
Dr. Stephen C. Newman



Dr. Heather-Jane Au



Dr. Alan Lees



Dr. Ambikaipakan Senthilselvan

Nov 25, 2002

ABSTRACT

A retrospective cohort study using two administrative databases was undertaken to assess whether demographic factors, particularly location of residence at diagnosis, influenced referral of breast cancer cases to specialized oncology centers. 1389 cases were identified from the population based Alberta cancer registry. Data from cancer registry were combined with appointment data from the AXON database. Cases were grouped according to whether they had an appointment, the indicator of referral. Logistic regression determined factors most likely to result in no appointment. Breast cancer specific survival analysis determined if having no appointment affected survival.

Older age, location of residence, and not married status were statistically significant factors for no appointment. High stage, high grade, unknown grade, and non-standard local treatment were statistically significant for poor survival. The no appointment group was significant to survival in those with unknown grade. Age 70 or over was significant to survival in those with unknown stage.

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Dedication

This is dedicated to the memory of all those who have died with cancer,
especially my father, Wilfrid, my brother, John, and my husband, Gordon.

Table of Contents

Chapter 1 - Introduction	1
1.0 Introduction to Thesis Topic.....	1
1.1 Study Objectives.....	1
1.2 Study Hypothesis.....	2
1.3 Incidence and Mortality of Breast Cancer.....	2
1.4 Risk Factors for Developing Breast Cancer.....	5
1.5 Breast Cancer as a Disease.....	6
 Chapter 2 - Literature Review - Breast Cancer Referral	 11
2.1 Clinical Practice Guidelines.....	11
2.1.1 Diagnosis	13
2.1.2 Treatment	14
2.1.3 Local Treatment.....	14
2.1.4 Systemic Treatment.....	17
2.2 Possible Factors that Bias Treatment.....	21
2.2.1 Age.....	22
2.2.2 Marital Status.....	25
2.2.3 Location.....	25
2.3 Problems in Breast Cancer Research.....	27
2.4 Key Studies.....	28
2.5 Conclusion.....	29

Chapter 3 - Materials and Methods

31

3.0	Introduction	31
3.1	Data Sources.....	31
3.1.1	Alberta Cancer Registry.....	31
3.1.1.2	Data Quality.....	33
3.1.2	Appointment Data	35
3.2	Participant Selection	37
3.3	Data Merger	38
3.4	Group Designation	39
3.5	Statistical Analysis	40
3.5.1	Variable Selection.....	40
3.5.2	Descriptive and Univariate Analysis	45
3.5.3	Logistic Regression.....	45
3.5.4	Survival.....	48

Chapter 4 - Descriptive Characteristics and Univariate Results

58

4.0	Introduction.....	58
4.1	Descriptive Characteristics of the Breast Cancer Cohort.....	58
4.1.1	Group with Appointment $\leq$ 90 Days	58
4.1.2	Group with No Appointment.....	65
4.1.3	Group with Appointment $>$ 90 Days.....	71
4.1.4	Comparison by Cross Tabulations Between the Three Appointment Groups	76
4.2	Results of Univariate Logistic Regression	86
4.3	Testing Model Robustness by Addition of Late Appointment Group	90

Chapter 5 - Multiple Logistic Regression Analysis **91**

5.0	Introduction.....	91
5.1	Selection of Variables for the Logistic Regression Model.....	91
5.2	Investigator Controlled Stepwise Logistic Regression	93
5.3	Automatic Forward Stepwise Logistic Regression	95
5.4	Investigator Controlled Logistic Regression Model	95
5.4.1	Interaction Variables	97
5.4.2	Goodness of Fit of the Logistic Regression Model.....	97
5.4.3	The final Model.....	98
5.5	Measure of Robustness of the Model	99
5.6	Conclusion.....	101

Chapter 6 - Survival Analysis **115**

6.0	Introduction to Survival Analysis.....	115
6.1	Kaplan-Meier Survival Analysis.....	116
6.2	Proportional Hazards Assumption.....	117
6.3	Cox Survival Analysis.....	120
6.3.1	Univariate Cox Survival Analysis.....	121
6.3.2	Investigator Controlled Cox Survival Analysis.....	122
6.3.3	Interaction Factors.....	124
6.4	The Final Model.....	125
6.5	Tests of Model Robustness	126
6.6	Conclusion.....	127

Chapter 7 - Discussion **145**

7.0	Introduction.....	145
7.1	Review of Multivariate Results	145
7.2	Which Group: Appointment or No Appointment?.....	147

7.2.1	Age.....	147
7.2.2	Marital Status.....	153
7.2.3	Location.....	154
7.2.4	Stage.....	157
7.3	Survival.....	159
7.3.1	Group.....	160
7.3.2	Stage.....	161
7.3.3	Age.....	162
7.3.4	Marital Status	163
7.3.5	Location	164
7.4	Database Analysis.....	165
7.5	Strengths and Limitations.....	166
7.5.1	Strengths of Present Study.....	167
7.5.2	Limitations of Present study.....	168
7.6	Areas of Further Research	168
	Bibliography	174
Appendix I	Letter from Alberta Cancer Registry to Physicians	184
Appendix II	American Joint Committee on Cancer Staging Guidelines.	187

List of Tables

Table 1.1	Estimated Incidence and Mortality by Age Group	10
Table 2.1	Projected Trends in Numbers of Females 70 and Over	30
Table 3.1	Appointment Groups	51
Table 3.2	Time from Diagnosis to First Appointment	52
Table 3.3	Demographic and Location Variables	53
Table 3.4	Disease Variables	55
Table 3.5	Treatment Variables	56
Table 3.6	Vital Status Variables	57
Table 4.1	Cross Tabulations of Marital Status, Stage, Grade, and Morphology within Three Age Groups for Group with Appointment ≤ 90 Days..	61
Table 4.2	Cross Tabulations of Location Variables within Three Age Groups for Group with Appointment ≤ 90 Days.....	62
Table 4.3	Cross Tabulations of Surgery Type and Radiation within Three Age Groups for Group with Appointment ≤ 90 Days	63
Table 4.4	Cross Tabulations of Systemic Therapy within Three Age Groups for Group with Appointment ≤ 90 Days	64
Table 4.5	Cross Tabulations of Cause of Death within Three Age Groups for Group with Appointment ≤ 90 Days	64
Table 4.6	Characteristics of the No Appointment Group	67
Table 4.7	Location of the No Appointment Group.....	68
Table 4.8	Comparison of Surgery, Surgical Type, Standard Local Treatment, and Systemic Treatment Between the Three Age Groups in Non- Referred Group.....	69
Table 4.9	Cause of Death by Three Age Groups in the No Appointment Group.....	70

Table 4.10	Cross Tabulations of Age, Marital Status, Stage, Grade, and Morphology within Three Age Groups for Group with Late Appointment.....	73
Table 4.11	Table of Proportion of Cases in the Late Appointment Group from Each of the Five Locations.....	74
Table 4.12	Cross Tabulations of Three Category Age Group by Surgery, Type of Surgery, and Radiation after Breast Conserving Surgery for the with Late Appointment Group.....	74
Table 4.13	Comparison of Patients Receiving Systemic Treatment with Chemotherapy and/or Hormone Therapy for three Age Groups in Late Appointment Group	75
Table 4.14	Comparison of Cause of Death in Three Age Groups for Late Appointment Group	75
Table 4.15	Cross Tabulations of Age Group and Marital Status by Appointment Group	81
Table 4.16	Cross Tabulations of Location by Appointment Group	81
Table 4.17	Cross Tabulations of Disease Variables by Appointment Group....	82
Table 4.18	Cross Tabulations of Standard Local Treatment by Appointment Group	83
Table 4.19	Cross Tabulations of Systemic Treatment by Appointment Group ..	83
Table 4.20	Cross Tabulations of Treatment by either Radiation Therapy and/or Chemotherapy by Appointment Group	84
Table 4.21	Cross Tabulations of Vital Status and Cause of Death by Appointment Group	84
Table 4.22	Cross Tabulation of Standard Local Treatment by Location For All Three Appointment Groups	85
Table 4.23	Cross Tabulation of Systemic Treatment with either Chemotherapy and/or Hormone Therapy by Location For All Three Appointment Groups	85

Table 4.24	Univariate Logistic Regression of Variables. Likelihood of being In the No Appointment Group versus the Appointment Group ...	88
Table 4.25	Univariate Logistic Regression for Location. Likelihood of being In the No Appointment Group versus the Appointment Group	89
Table 5.1	Cross Tabulation of Appointment Group by Stage	105
Table 5.2	First Step of Investigator Controlled Regression, Age Entered	105
Table 5.3	Second Step of Investigator Controlled Regression, Marital Status Entered	106
Table 5.4	Third Step of Investigator Controlled Regression, Morphology Entered	106
Table 5.5	Fourth Step of Investigator Controlled Regression, Grade Entered.....	107
Table 5.6	Fifth and Final Step of Investigator Controlled Regression, Location Entered	108
Table 5.7	Final Step of Automatic Forward Stepwise Logistic Regression as Computed by SAS	109
Table 5.8	Investigator Controlled Multivariate Model Predicting that a Patient Would be Part of the No Appointment Group. Final Model	110
Table 5.9	Hosmer and Lemeshow Goodness of Fit Test for the Logistic Regression Model	111
Table 5.10	Testing Model Robustness, 83 Late Cases Added to Appointment Group	112
Table 5.11	Testing Model Robustness, 83 Late Cases Added to No Appointment Group	113
Table 5.12	Test of Stage, Known or Unknown, as a Proxy for Appointment Status	114

Table 6.1	Univariate Kaplan-Meier Survival Analysis - Breast Cancer Death Specific	129
Table 6.2	Univariate Cox Survival Analysis - Variables that Satisfy The Proportional Hazards Assumption.....	140
Table 6.3	Initial Investigator Controlled Multivariate Cox Survival Analysis..	141
Table 6.4	Final Investigator Controlled Cox Survival Analysis	142
Table 6.5	Testing for Robustness of Final Investigator Controlled Cox Survival Analysis - Late Cases Added to Appointment Group...	143
Table 6.6	Testing for Robustness of Final Investigator Controlled Cox Survival Analysis - Late Cases Added to No Appointment Group..	144
Table 7.1	Cross Tabulation of Marital Status with Age Category, Stage, Grade, and Group	172
Table 7.2	Cross Tabulation of Location with Age Category, Stage, Grade, and Group	172
Table 7.3	Cross Tabulation of Three Category Stage by Age Group, Marital Status and Location for the Whole Cohort.....	173

List of Figures

Figure 1.1	Age Standardized Incidence Rate of Breast, Lung, and Colo-rectal cancer, 1973 - 2002	8
Figure 1.2	Age Standardized Mortality Rate of Breast, Lung, and Colo-rectal cancer, 1973 - 2002	8
Figure 1.3	Five Year Survival from Breast, Lung, and Colo-rectal Cancer	9
Figure 1.4	Comparison of Age Standardized Incidence Rates and Age Standardized Mortality Rates in Different Parts of the World	9
Figure 2.1	Projected Number Canadian Women 70 and over with Breast Cancer from 2001 to 2026	30
Figure 3.1	Criteria for Inclusion or Exclusion from the Study	51
Figure 3.2	Map of Alberta: the Five Location Categories by Regional Health Authority	54
Figure 6.1	Log minus Log Survival Distribution Function for Appointment Group	130
Figure 6.2	Log minus Log Survival Distribution Function for Three Category Age	131
Figure 6.3	Log minus Log Survival Distribution Function for Two Category Age	132
Figure 6.4	Log minus Log Survival Distribution Function for Marital Status:	133
Figure 6.5	Log minus Log Survival Distribution Function for Three Category Stage	134
Figure 6.6	Log minus Log Survival Distribution Function for Three Category Grade	135
Figure 6.7	Log minus Log Survival Distribution Function for Two Category Morphology	136
Figure 6.8	Log minus Log Survival Distribution Function for Five Category Location.....	137

Figure 6.9	Log minus Log Survival Distribution Function for Standard Local Treatment	138
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Figure 6.10	Log minus Log Survival Distribution Function for Systemic Treatment	139
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Chapter 1- Introduction

1.0 Introduction to Thesis Topic

The treatment of breast cancer is complex. Surgery for early stage breast cancer may now be accomplished with breast conserving techniques that were not used in the past. This surgery is usually followed by radiation therapy to maintain good local control. Systemic spread, in cases deemed at risk, is contained by chemotherapy and/or hormonal therapy. Hormone therapy can be prescribed by the surgeon or family physician, but chemotherapy and radiation therapy are given under the supervision of medical and radiation oncologists, specialists in their fields. These specialists are located at specialized cancer investigation and treatment centers under the auspices of the Alberta Cancer Board and a referral is necessary to enlist their support.

There has been concern that some patients are not given the benefit of specialist consultation due to demographic factors, especially age and location of residence. The objective of this thesis is to determine if there is any ground for such concern. In addition, an analysis will be done to determine if non-referral affects survival. These questions will be answered by a study using an administrative database and the Alberta Cancer Registry.

1.1 Study Objectives

The main objective of this thesis was to determine bias in referral of breast cancer patients to specialized consultation and treatment services in Alberta, by a systematic exclusion of some groups of patients based on socio-demographic, clinical, and/or tumour factors. A secondary objective would be to determine if the excluded groups

of women have poorer survival than those who are referred. A third objective is to determine whether these objectives can be accomplished using administrative databases.

1.2 Study Hypothesis

The null hypothesis is that there is no bias in referral patterns and therefore no bias affecting survival. The alternative hypothesis, the basis of this study, is that there are variations in referral patterns based on demographic characteristics such as age, location of residence, socio-economic status, education, and marital status. In particular, it is postulated that patients who are over age 70, or those living in more remote locations of the province would be less likely to be referred.

A second hypothesis, arising from the first, is that referral is associated with better survival than not being referred.

Finally, it is proposed that data available within two Alberta Cancer Board databases, the Alberta cancer registry and the appointments data, would be sufficient to answer the first two questions about possible referral bias and subsequent survival, without chart review.



1.3 Incidence and Mortality of Breast Cancer

In Canada, breast cancer is the most frequently diagnosed cancer in women, representing more than 25% of all female cancer diagnoses. In 2002, an estimated 20,500 women across Canada, 1,750 in Alberta, will develop breast cancer¹.

Figure 1.1 shows the increase in the age-standardized incidence rate in the time period between 1973 and 2002 for breast cancer with comparable rates for colorectal and lung cancer. The rate for breast cancer has risen from 82.2 to 106 per one hundred thousand women. The incidence of lung cancer has risen dramatically among women from 12.9 in 1973 to 47.3 in 2002, while the incidence of colorectal cancer has decreased from 46.2 to 39.2 in the same time period ¹. Age-standardization is a method to minimize the effects of differences in age composition when comparing different populations ². The lifetime likelihood of developing breast cancer is 1/9 for Canadian women ¹.

Figure 1.2 gives a similar illustration of the change in the age-standardized mortality rate for breast cancer, lung, and colorectal cancer. In the time period from 1973 - 2002, the age-standardized breast cancer mortality rate has decreased from 31.4 to 25.6 per one hundred thousand women. Breast cancer is no longer the leading cause of cancer related death in women, being superceded by lung cancer. An estimated 5,400 women in Canada and 420 in Alberta, will die of breast cancer in 2002. The mortality rate for lung cancer has risen from 10.9 to 37.8, while that of colorectal cancer has decreased from 24.3 to 13.6 ¹.

Figure 1.3 illustrates the change in five year relative survival rates for breast, colorectal and lung cancer between 1974 - 1998. The five year relative survival rates for breast cancer have risen significantly in Alberta from 75% patients alive at five years post diagnosis (95% confidence interval 72.7% - 76.6%) for the period between 1985 and 1987, to 83.8% (95% confidence interval 82.1% - 85.5%) for the period from 1994 - 1996 ³. These are consistent with the 1992 Canadian five-year survival of 82% (95% confidence interval 81% - 83%) ⁴. Breast cancer illustrates a good five year survival, while that of colorectal cancer is fair, rising from 53% to 58% from 1985 to 1996 in Alberta, and the five year survival for lung cancer is poor at 12.6% with no change from 1985 to 1996 in Alberta ³. The Alberta and Canadian statistics are also similar to those of the National Cancer Institute' Surveillance,

Epidemiology, and End Results (SEER) sample, comprising approximately 10% of the total American population, which showed a 74.7% breast cancer five year survival in 1974 rising to 86.2% in 1995 ⁵. There are differences between both countries and regions within countries. For instance, within Canada, British Columbia has the highest five-year survival (85%), while Newfoundland has the lowest (76%), but British Columbia has the highest reported proportion of women who have had a mammogram (69%) while Newfoundland has the lowest reported rate (43%) ⁴.

Even with a declining mortality rate and an increased five-year survival, breast cancer is second to lung cancer as the most frequent cause of cancer death among women because it is the most common cancer in women and both the incidence and the absolute number of cases are increasing. The potential years of life lost (PYLL) by women in a year due to breast cancer in Canada (94,000 years) is second only to lung cancer (110,000 years) ¹.

Figure 1.4 illustrates the differences in incidence and mortality rates for breast cancer throughout the world. Both incidence and mortality rates vary widely. Comparisons are quite complex because of population screening and standardized reporting, prevalent practices in North America and Western Europe, but not in developing countries. Keeping this in mind, North American and Western European women are at higher reported rate for developing breast cancer than women elsewhere ⁶. Asian women seem to have the lowest reported rate. The highest rate is more than five times the lowest ⁷.

1.4 Risk Factors for Developing Breast Cancer

Table 1.1 shows the risk of incidence and death from breast cancer by age groups. The most important risk factors for breast cancer are age and being female. The incidence of breast cancer rises steadily with age from 4.6 per 100,000 women in the third decade of life (20-29), to 429.3 per 100,000 women in the eighth decade (75-79), with a leveling off after that. In Canada 2002, an estimated 78% of new cases will be in women over the age of 50 with 31% being in women over 70. An estimated 86% of deaths will be in women 50 and over while 52% will be in women 70 and over ¹. The increase in incidence and death that occurs from breast cancer as a function of a woman's age is also reported from other countries ^{8,9}.

Other risk factors for developing breast cancer include early menarche, later age at first pregnancy, low parity, and late menopause ^{7,10,11}. Risk factors change with age. Among women under 45, risk factors include late age at last birth, high parity, and recent use of oral contraceptives. At older ages risk factors include late age at first birth and low parity. At all ages, there was an increased risk of breast cancer associated with difficulty in conceiving, benign breast disease, not having breast fed, and a family history of breast cancer ^{12,13}.

A family history of breast cancer including especially: more than one affected relative, bilateral breast cancer, breast and ovarian cancer in the same woman, breast cancer at age ≤ 35 , and male breast cancer, is associated with an increased risk for breast cancer ¹⁴⁻¹⁸. This type of family history can be indicative of genetic predisposition caused by gene mutations in either the BRCA1 or BRCA2 genes. Mutations in these genes is associated with an increased likelihood of breast cancer for an individual ¹⁷.

Numerous lifestyle patterns, including adiposity ^{19,20}, increased consumption of beef, pork, and sweet deserts ²¹, use of birth control pills in young women ^{22,23}, hormone

replacement therapy²⁴⁻²⁶, higher socio-economic status, and alcohol intake²⁷, have been associated with an increase in breast cancer incidence. Physical activity is associated with a reduced risk^{28,29}.

1.5 Breast Cancer as a Disease

Breast cancer is a heterogeneous disease and can have widely differing outcomes. It may have a long natural history and be present in the breast for some years before it becomes clinically apparent or it may spread more rapidly to regional and distant sites. Prognostic indicators for breast cancer include tumour size, histologic grade, and the number of involved axillary lymph nodes. These are the basis for the Nottingham Prognostic Index, a validated score that can give both the relative and the absolute risk for a patient with operable breast cancer. This can aid in the decision to use systemic adjuvant cytotoxic chemotherapy^{25,30,31}. Menopausal status and hormone receptor status are also prognostic and a positive estrogen receptor status in a menopausal woman is associated with a good prognosis and good response to treatment with systemic hormone therapy, tamoxifen^{30,32,33}. Gene expression as in p53, and HER2 analysis influences prognosis and treatment^{30,34,35}.

Recurrence and distant metastases have occurred within months to decades after local control was achieved. Therefore, it is difficult to state that the disease is ever cured. With present day surveillance and treatment strategies, many women treated for breast cancer will live out their predicted life span without ever having a recurrence.

From the time of Hippocrates, it has been debated whether breast cancer is essentially a local or a systemic disease. Believing that breast cancer was basically a local disease that only metastasized after regional invasion, Halsted pioneered the radical mastectomy for breast cancer at the end of the nineteenth century. This was to gain control of the local disease and ultimately benefit survival. This offered the first bit

of hope in the treatment of a disease that had been considered universally hopeless prior to this time. It involved extensive surgery and occasionally recurrence occurred in spite of this. The idea that breast cancer might be inherently systemic or local at the outset arose because of the cases that recurred. Fisher most clearly articulated this view, stating that while some cases had occult metastases at the outset, other cases were local in nature and were unlikely to ever metastasize. This resulted in efforts to identify cases that might benefit from systemic treatment and in less mutilating surgery for local disease, because the local treatment was unlikely to influence survival ³⁶.

At the present time, treatment for breast cancer is both local and systemic and often involves multi-modality therapy necessitating both surgical and oncologic specialists. This thesis is a study of factors that might mitigate against a woman being referred to an oncologist after surgery.

Figure 1.1: Comparison of Age-Standardized Incidence Rates per 100,000 Women (ASIR) for Three Major Cancers, for 1973, 1983, 1993, and 2002 ¹

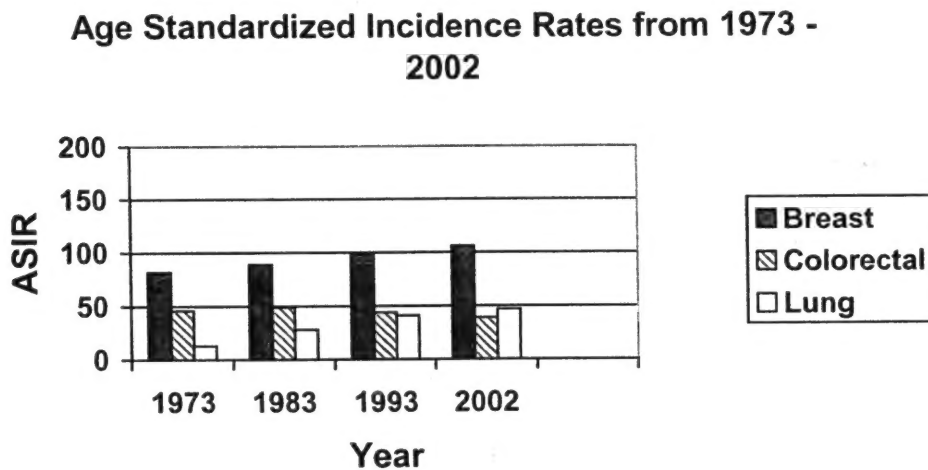


Figure 1.2: Comparison of Age-Standardized Mortality Rates per 100,000 women (ASMR) for Three Major Cancers from 1973 - 2002 ¹.

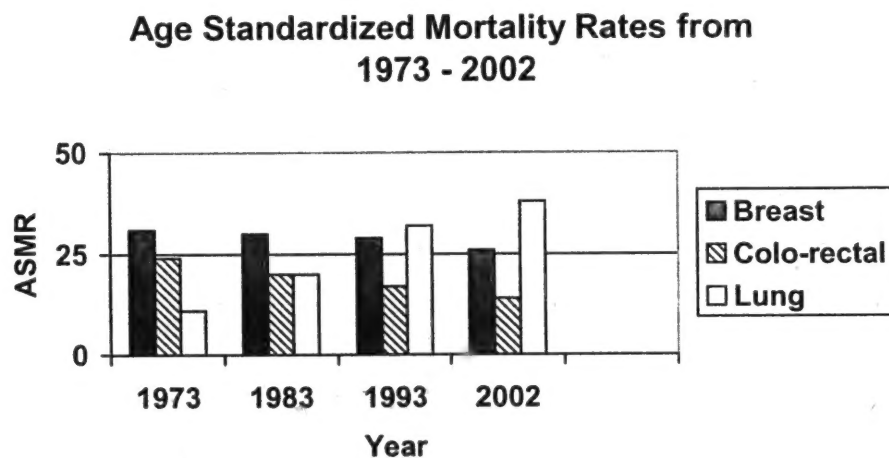


Figure 1.3 Comparison of 5-year survival for breast, colorectal, and lung cancer from 1985 - 1996.³

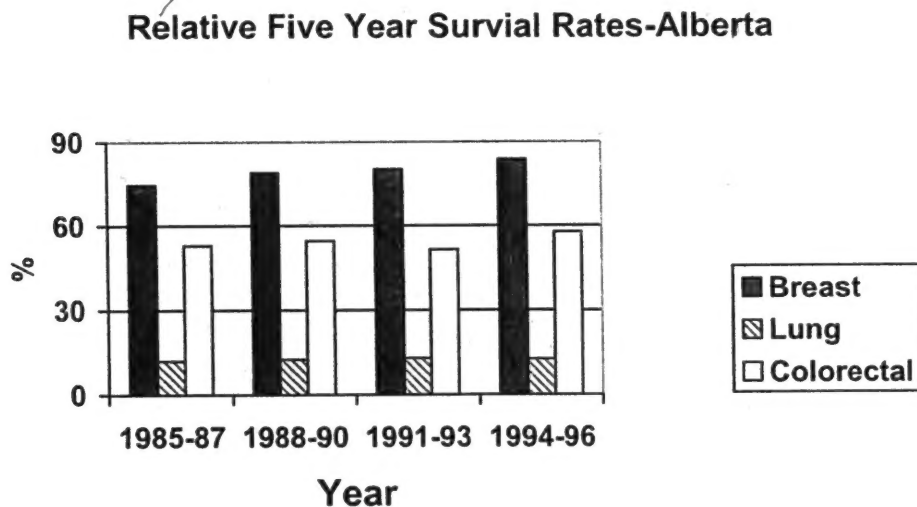


Figure 1.4 Comparison of Age Standardized Incidence and Mortality Rates for Breast Cancer in Different Areas of the World.⁶

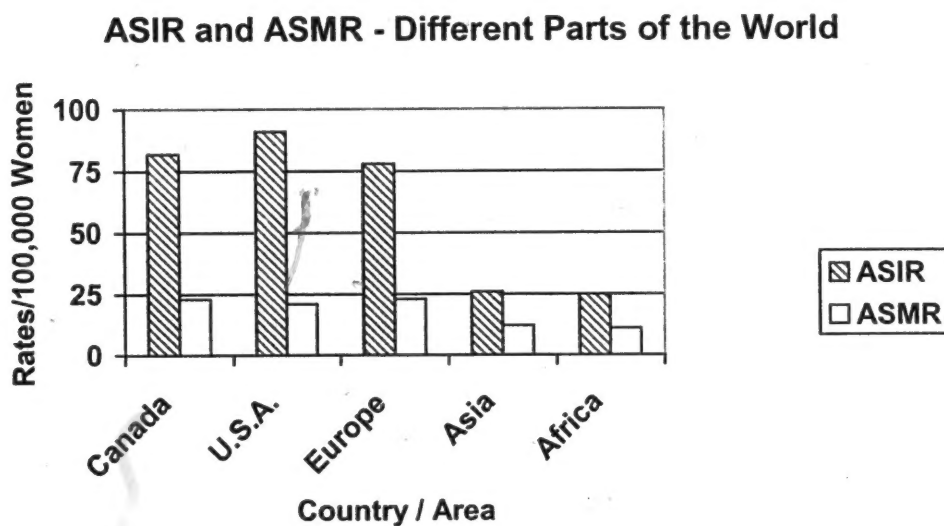


Table 1.1: Estimated Distribution of New Breast Cancer Cases and Deaths Due to Breast Cancer by Age Group in 2002, Canada, from Surveillance and Risk Assessment Division CCDPC, Health Canada, ¹.

Age Group	% New Cases	% Deaths
< 50	22%	13%
50-69	47%	35%
≥70	31%	52%

Chapter 2 - Literature Review - Breast Cancer Referral

This chapter presents a review of published literature on treatment, referral patterns for breast cancer, and survival outcomes. Several variables affecting treatment and referral will be presented. Key studies will be identified and problems pertaining to this area of research will be discussed.

Literature searches were conducted in Medline and Pubmed. The searches were divided into key areas. Using the word 'breast cancer' in all searches, other key words or phrases were added depending on the main topic of the search. These included 'clinical practice guidelines', 'meta-analysis', 'age', 'comorbidity', 'geographic variation', 'specialist referral', 'practice pattern variation', 'radiation therapy', 'adjuvant therapy', and 'survival'. Reference lists of the found materials were also scanned. Because of the volume of literature, only studies after 1980 were sought.

2.1 Clinical Practice Guidelines

In the interests of effective clinical practice and improved health outcomes, and because of the variations in treatment in different regions of a country, clinical practice guidelines for the treatment of breast cancer have been developed in several countries. Guidelines were in place in Alberta in 1997 from an Alberta Cancer Board Research meeting-symposium organized by the Breast Group of Alberta in Calgary, and held in November of 1996. In addition, draft copies of the 1998 Canadian clinical practice guidelines were available³⁷. Other countries that had clinical practice guidelines already in place included the United Kingdom, 1986³⁸, the United States, 1991³⁹, France, 1993-94⁴⁰, and Australia, 1995⁴¹. This paper will focus on the Canadian clinical practice guidelines.

The Australian and the Canadian clinical practice guidelines were based on 'best evidence' from systematic reviews of the literature. Evidence was categorized according to the strength of the studies from which it came. Level 1 evidence is given the most weight ⁴¹.

Level 1: obtained from systematic review of all randomized controlled trials

Level 2: obtained from at least 1 randomized controlled trials.

Level 3: from other kinds of well designed studies

Level 4: opinions of respected authorities, descriptive studies, and expert committees.

Clinical practice guidelines not only influence practice, their use may affect survival. They are developed in accordance with strict standards and can form a trusted reference to inform health professionals of the overall results of trials of investigation and treatment. In turn, the professional can communicate and discuss this knowledge with the patient, ultimately involving her in treatment decisions ³⁷.

Clinical practice guidelines have mainly been developed for treatment of 'early' breast cancer, the most common presentation. Other guidelines deal with a number of topics including lymphoedema, hormone replacement, pain, and sentinel node biopsy. Some of these would apply to the management of later cancer. Early cancers are less than five centimeters in diameter, with or without positive, movable axillary nodes, which conforms to Stages I and II as defined by UICC and AJCC standards, or T1-2, N0-1 M0 by tumor-node-metastases staging ⁴². Treatment, in addition to surgery alone, has been shown to significantly prolong both disease-free and disease specific survival. Disease free survival is the time span between initial diagnosis and recurrence while disease specific survival is the time between initial diagnosis and death from breast cancer.

2.1.1 Diagnosis

When breast cancer is suspected, either because of a palpable lump or from mammography findings, the clinical practice guidelines recommend a thorough patient work-up to assess the extent of the disease and verify the diagnosis. A complete clinical assessment, followed by mammography or ultrasound, gives information on extent of tumor, spread to nodes and opposite breast, possible metastases, and general physical condition. The diagnosis must be confirmed by either cytology or histology. Fine needle aspiration would provide a suspension of cells for a cytological diagnosis while core biopsy would provide a cone of tumour tissue for histologic diagnosis. Both procedures can be performed on an outpatient basis and both may provide enough tissue to determine the hormone receptor status of the tumour, although sometimes the fine needle aspiration does not provide enough tissue ⁴¹. If neither of these procedures have been done and there is still a strong clinical suspicion of malignancy, an open biopsy should be done to establish a pre-operative diagnosis. These procedures are not for treatment, but rather for diagnostic purposes. They provide information about morphologic type of tumour, its size, grade, and hormone receptor status ⁴³.

Determining tumour status and extent prior to treatment allows for discussion about management plans with the patient. There are alternative forms of therapy and women are encouraged to participate in treatment decisions. Prior to the present era, when there were fewer alternatives, the diagnostic biopsy and definitive surgery often occurred in the same operation.

2.1.2 Treatment

Treatment for breast cancer is both local and systemic. Local treatment is for the tumor itself and any regional lymph nodes. Local treatment is usually surgery to the breast and axillary lymph nodes. Radiation to the breast is necessary after breast conserving procedures and may also be indicated after complete removal of the breast. The goals of local treatment are local control, cosmetic result, a minimum of psychosocial impact, and the hope of total control^{37, 39, 41}. The outcome measure of success is non-recurrence of local disease.

Systemic treatment for early breast cancer is called systemic adjuvant therapy. This is the use of medications to stop, or significantly slow, the growth of occult micrometastases that may already have spread from the tumour to other areas of the body. Systemic adjuvant therapy includes chemotherapy and hormone therapy. The primary measures of success are an increase in the length of disease free and disease specific survival. A secondary measure of success is an acceptable level of side effects.

2.1.3 Local Treatment

The results of review of five individual randomized control trials and a meta-analysis of the Early Breast Cancer Trialists are consistent in showing that breast conserving surgery with radiation is equivalent in outcome to total mastectomy (level I evidence)⁴⁴. Radiation therapy to the breast after breast conserving surgery significantly reduces the risk of local recurrence.

Breast conserving surgery is defined as excision of the primary tumor along with a cuff of normal tissue while preserving the cosmetic appearance of the breast³⁷. It is also known as complete local excision, lumpectomy, wide local excision, segmental mastectomy, or partial mastectomy. Complete excision of the cancer is an essential

requirement of breast conserving surgery and may require a second conserving operation or progression to complete mastectomy to obtain clear margins. Radiation therapy to the breast should follow breast-conserving surgery. If not accompanied by radiation, the incidence of local recurrence after breast conserving surgery is significantly increased ⁴⁴.

Total mastectomy is removal of the entire breast without taking the underlying pectoralis muscles. Radiation therapy to the chest wall may not be necessary following total mastectomy unless there is a high risk of loco-regional recurrence. Neither breast conserving surgery nor total mastectomy usually require post-operative radiation to the axilla or other lymph node areas, but it is given if there is a high risk of loco-regional recurrence.

Both total mastectomy and breast conserving surgery should be accompanied by axillary dissection of level 1 and level 2 nodes for accurate staging and to reduce the incidence of recurrence in the axilla ⁴⁵. Axillary dissection is removal of the lymph nodes in the axilla. The extent of the dissection is defined with reference to the pectoralis minor muscle. Level 1 nodes are lateral to or below the lateral border of the pectoralis minor muscle. Level 2 nodes are deep to the pectoralis minor muscle and receive lymph from level 1 nodes and also directly from the breast. Level 3 nodes lie medial to the pectoralis minor muscle in the infraclavicular fossa. They receive lymph from the previous levels and also from the superior part of the breast ⁴⁵.

More recent Canadian clinical practice guidelines cautiously recommend the use of sentinel lymph node biopsy for some cases in very prescribed circumstances. Sentinel lymph node biopsy is the removal of one or two lymph nodes that have been traced from injection of dye or radioactive material into the breast tissue surrounding the tumour. These sentinel nodes are thought to represent the histologic status of the whole lymphatic basin. There is a high risk of false negative in inexperienced hands. The procedure is followed by axillary dissection if the sentinel node is positive ⁴⁶.

Axillary dissection is done not only as a staging procedure and to eradicate metastases within the nodes, it is also used to determine the need for systemic adjuvant and sometimes radiation therapy, and to determine if further staging investigations (chest x-ray, liver ultrasound, and bone scan) are necessary. If this knowledge will not contribute to treatment decisions because of factors such as comorbidity or age, and the nodes are clinically negative, the Canadian guidelines suggest that neither axillary dissection nor further staging investigations may be necessary^{45,47}. United Kingdom guidelines recommended axillary sampling, not dissection. This had been discouraged as inadequate in the other guidelines. The UK guidelines recommended treatment based on age rather than node status³⁸.

The choice between total mastectomy and breast conserving surgery plus radiation is sometimes a medical decision based on the size or extent of the tumour, breast size, and cosmetics that can be technically achieved. In many cases though, it can be the patient's preference, based on her needs and circumstances. Total mastectomy may not need to be followed with radiation therapy and therefore, may not be as time consuming. This might work best for a woman who does not live close to facilities for radiation therapy.

More recent evidence, not available at the time of this study, has shown that while radiation therapy consistently reduces the likelihood of local recurrence by about two-thirds, its effect on overall survival varies between patient groups. This analysis was of 40 unconfounded trials begun prior to 1990 and involving 20,000 women. The trials were unconfounded because treatment with radiation was compared to the same treatment without radiation. While post-operative radiation therapy, after year two, did reduce breast cancer deaths by about 13 %, it increased death rates from other causes, particularly cardiovascular causes, by about 21.2 %. Those who were most likely to get a net benefit from radiation therapy are the young and those at high risk. The older patient and those with a low local recurrence risk are likely to have an

overall net increase in mortality after radiation therapy because of an increase in cardiovascular deaths.

This mortality risk appears to increase in successive decades after the breast cancer treatment⁴⁸. These results may reflect practices that aren't commonly used now. For instance, in the majority of these trials, women were surgically treated with mastectomy and not just breast conserving surgery. In addition, in many of the trials, the irradiated fields included not only the breast, but also the axilla, the internal mammary chain, and the supra-clavicular nodes.

Another more recent British study has also demonstrated no difference to survival, in clinically equivalent cases, between axillary dissection or axillary sampling⁴⁹. Both sets of recent results may alter future guidelines and they may already have an effect on clinical practice. They illustrate the evolving nature of medical knowledge and practice and the fact that many decisions are not black and white in nature.

2.1.4 Systemic Treatment

Systemic treatment consists of the use of anticancer medications after initial surgical treatment of breast cancer⁵⁰. The use of anti-cancer medications after, and not prior to, initial surgical management is referred to as systemic adjuvant therapy. The two forms of systemic adjuvant therapy are chemotherapy (cytotoxic drugs) and hormonal therapy (tamoxifen and ovarian ablation). The different forms of systemic adjuvant therapy are indicated depending on tumour hormone receptor status, patient age, risk status, and side effects.

The Canadian clinical practice guidelines recommend that high and intermediate risk women under age 50, and women between the ages of 50 and 69 who are estrogen receptor negative, be offered combination chemotherapy. For high or intermediate

risk women between the ages of 50 and 69 who are estrogen receptor positive; and high risk women 70 and over, the guidelines recommended adjuvant hormonal treatment with tamoxifen^{50, 51}. The new 2001 guidelines do not recommended tamoxifen for women over 70 who are estrogen receptor negative³².

Prognosis, or patient risk of recurrence or death, is assessed by many characteristics. These include tumour size, grade, axillary lymph node status, estrogen receptor status, lymphatic or vascular invasion, and age younger than 35.

The Canadian, American, and Australian guidelines all cited the 1990 Early Breast Cancer Trialists Collaborative results, a meta-analysis of 133 trials involving 75,000 women⁵². These results indicated that chemotherapy, tamoxifen, and ovarian ablation all reduced the risk of recurrence and death in women under 50 for both node positive and node negative cancer. Chemotherapy and tamoxifen also work in women over 50 although ovarian ablation does not^{41, 50}. More recent results from the Early Breast Cancer Trialists' Collaborative Group further extends the benefits of polychemotherapy, from women under 50 to those 50-69, from those with node-positive disease to those with node-negative disease, to those who are also treated with tamoxifen, and to those who are hormone receptor negative⁵³.

Chemotherapy has a high incidence of side effect and may be very difficult to tolerate. Chemotherapy destroys cells that are dividing rapidly including tumour cells and normal body cells. Because of the effect on normal cells, patients commonly suffer fatigue, nausea, vomiting, diarrhea, and hair loss. Anemia, infection, and bleeding are also possible. Though not common, subsequent hematological malignancies are increased by some chemotherapy regimes.

Four factors are considered in the prescription of chemotherapy: the prognosis without the therapy, improvement in prognosis with therapy, side effects and comorbidity. Low-risk patients, such as those with node negative, stage I cancer, are

more likely to be cured by local treatment without any systemic therapy. Instruments, such as the Nottingham Prognostic Index for primary breast cancer, help to quantify patient risk. This particular index is based on tumour size, stage, and tumour grade³¹. While the proportional benefit of chemotherapy is the same for all patients, the absolute benefit is less for low-risk patients. If the relative improvement in the five-year mortality rate is 20%, then the absolute improvement in five-year mortality for a low risk patient would be 2%, reducing the hazard ratio from 10% to 8% and improving the prognosis from 90% to 92%. A high risk patient with a five-year mortality risk of 50% would decrease that risk to 40%. So the absolute improvement in 5-year mortality would be 10%, having risen from 50% to 60%. Therefore, the absolute improvement in prognosis is much greater for high-risk patients although both high and low risk have the same 20% relative improvement. The decision to use chemotherapy can be difficult for the individual patient and her physician. Chemotherapy is rarely considered in women 70 years of age or older.

Tamoxifen, a hormonal therapy, is usually very well tolerated. The most common side effect is hot flashes. Other, less frequent risks include endometrial cancer, venous thromboembolism, and cataract. However, the benefits usually offset the side effects. Ovarian ablation is an older form of hormonal therapy, recently revisited, that is of value to some pre-menopausal patients⁵⁰. The newer form of temporary ovarian ablation using an ovarian suppressant, luteinizing hormone releasing hormone, is both effective and without major side effects, although there is still a risk for hot flushes⁵⁴.

Tamoxifen use was analysed in 30,000 women in 40 trials⁵². Although improvement in disease free and overall survival in many individual trials was not statistically significant, collectively, the effects were significant. The absolute benefits of tamoxifen are greater for node positive women, but it benefits both node positive and node negative women. Disease free and overall survival are improved in women who are hormone receptor positive but not in those who are hormone receptor negative.

Disease free survival was statistically significant in all women, but better for those over the age of 50. There was statistically significant increased overall survival for women over 50. More recent results confirm that disease free and overall survival is improved regardless of age for estrogen receptor positive women, and that there is evidence of safety with respect to other causes of death⁵⁵. More prolonged therapy, from 2 to 5 years, generally lead to better outcomes⁵⁶.

The mortality difference between tamoxifen users and controls grows steadily bigger throughout years 1-10. At 5 years the absolute difference in survival is 3.6%. By 10 years the overall difference in survival is 6.2%, with 58.8% of tamoxifen but only 52.6% of control patients still alive. These results are combined for node-positive and node-negative patients. The benefits are greater for node-positive patients. The absolute improvement in survival at ten years is 8.2% for node-positive patients and 3.5% for node-negative patients⁵².

Ovarian ablation offers a statistically significant improvement in recurrence free survival and was the historic treatment for breast cancer. Ovarian ablation is more effective in women with hormone receptor positive tumors. There have been fewer studies of ovarian ablation but one randomized trial indicated that ovarian ablation was superior to chemotherapy in pre-menopausal patients with positive estrogen receptors⁴¹. However, the chemotherapy regime used in this trial was apparently not a standard adjuvant regime and has been shown to be substandard in the advanced cancer setting. Ovarian ablation is not indicated after menopause as studies have not shown any significant difference in survival between women over 50 who had ovarian ablation and those who did not. This is not surprising, considering that the mechanism is to induce menopause. For women under 50, the difference in recurrence free survival at 15 years is 10.6%, with 52.9% of ovarian ablation and 42.3% of controls free of recurrence (logrank test $p < 0.001$). The absolute difference in overall survival at 15 years was 10.2% (logrank test: $p < 0.001$). The effects are

greater for node positive women but are still statistically significant for node negative women.^{41, 54}

Age 70 and over comprises about 40% of all breast cancer cases but only accounted for one-tenth of the women in the tamoxifen trials. For women age 70 or over, tamoxifen was recommended even if the hormone receptor status was negative. Most of the guidelines did not recommend the routine use of cytotoxic chemotherapy for women over 70. The Canadian Medical Association clinical practice guidelines note that tamoxifen is the only form of adjuvant systemic therapy that has been adequately evaluated in women over 70 and so it is the only form of systemic therapy recommended in this age group outside of a clinical trial setting.

All of the clinical practice guidelines recommend that it is the patient herself, including the patient age 70 or over, who should ultimately make the decision about systemic adjuvant therapy after being adequately informed.

2.2 Possible Factors that Bias the Treatment of Women with Breast Cancer

Several factors influence decisions for the treatment of breast cancer. Among these are the age of the patient, their location of residence, and even their marital status. These measures can be ascertained from available databases and thereby form part of this study. There are other factors which cannot be read from a database. These include the physical and mental status of the patient, comorbid conditions, access to transportation, education, and at home support. In addition, the patients own thoughts and feelings about treatment along with those of her physician are not measured. In this section we will discuss the literature around some of the factors, especially those that are measurable from the database.

2.2.1

Age

Breast cancer is a disease of aging. The incidence increases from less than 200 to nearly 400 cases per 100,000 as age increases from forty to seventy-five⁵⁷.

Figure 2.1 and Table 2.1 both demonstrate the projected increase in the numbers of older breast cancer cases in the next quarter century. Population growth, population aging, and an increased incidence all contribute to both a relative and an absolute increase in the number of women ≥ 70 with breast cancer⁵⁷. In 2001, women 70 and over comprised just over 10% of the Canadian population. By 2026, they will comprise over 16% of the population⁵⁸. The actual numbers of breast cancer cases in Canada, in women aged 70 and over, will almost double from 6400 cases in 2001 to 11,600 cases in 2026^{57,58}. Therefore, breast cancer in older women will become an increasingly common problem.

The evidence suggests that people over the age of 70 are not investigated or treated as aggressively as younger patients. Older women are referred to specialists less often than their younger counterparts⁵⁹. In addition, they are less likely than younger women to be staged^{8,60,61}. Several reasons for this situation have been given.

The first reason given for less aggressive treatment and investigation of older women is that few studies have addressed these issues. Only the tamoxifen trials included women over the age of seventy. The clinical practice guidelines generally do not address radiation and chemotherapy in older women but do recommend tamoxifen. In addition, some studies, as detailed above, have questioned the value to survival of intensive investigation and treatment for older women. There is little evidence to support aggressive treatment.

A second reason given for the differential in treatment and investigation is that women in this age group are usually too frail or have too many other comorbidities. Comorbidity is the presence of other disease conditions with the breast cancer. Older women do have more comorbidities and are more severely affected by them than younger patients^{8, 61, 62}. Increasing comorbidity, not surprisingly, has been associated with less than standard treatment for breast cancer⁶³. This finding applies to both older and younger patients⁶⁴. However, many studies, controlling for comorbidity, have shown that it is chronological age itself that is associated with a significantly increased risk of receiving non-standard investigation and treatment^{8, 59, 61, 64-66}. In these studies, it is shown that older age has been used as a proxy for comorbidity and that elderly women with no comorbidity are still more likely to receive less than appropriate management of their breast cancer.

Greenfield⁶³, in a retrospective study of breast, colorectal, and prostate cancer patients, examined the appropriateness of treatment using a unique technique called 'Criteria Mapping'. This unusual methodology charts appropriate treatment for patients based on tumor characteristics, functional status, and comorbidity. The maps were first devised by oncologists and geriatricians and then reviewed by national experts before being implemented in the study. The criteria map accommodates multiple appropriate options and does not penalize physicians for minimal investigation and treatment of a medically unfit patient. 374 breast cancer patients from seven Southern California hospitals were stratified by age, hospital, and physician to provide a wide spectrum of practice styles and socio-economic status. There was no significant difference in stage at presentation between older and younger patients ($70 < , \geq 70$). However, patients in the older age group had significantly less axillary lymph nodes examined and were significantly less likely to have standard treatment. A sub-sample of this group, comprising patients with early stage cancer and no co-morbidity, had a significant number of patients who were not treated in a standard fashion. The conclusion from this study is that an age bias certainly exists.

A Canadian study by Hebert-Croteau ⁶⁴ found that age, controlling for comorbidity, is a significant predictor of non-referral to a specialist, limited or no axillary lymph node dissection, and no radiation therapy following breast conserving surgery. An American study of 1800 women over the age of 55 found that increased age resulted in an increase in unknown stage, and a decrease in axillary lymph node dissection, breast conserving surgery, and radiation therapy after breast conserving surgery, controlling for comorbidity. This study used the quality assured databases within six SEER (Surveillance Epidemiology and End Results - part of National Cancer Institute in the United States) affiliated cancer registries ⁸.

A third claim is that elderly women do not present at an early stage. This would be due to lack of screening programs for women over seventy, pre-existing comorbidity that masks the presentation of breast cancer, and lack of knowledge on the part of older women of the signs and symptoms of breast cancer. Despite these facts, several studies have shown that older women do not present at a later stage than younger women ^{59, 61, 63, 67, 68}.

A last reason given for less decisive treatment of older women with breast cancer is the perception that these women really do not want treatment. Both physician and societal attitudes underestimate normal life expectancy and studies have shown that physicians spend less time with their older patients and less often involve them in decision making ⁶⁹. In a study of patient perspectives on cancer treatment it was found that older women were less likely to be presented with alternative therapies than younger women (19% versus 31%), they were less likely to be offered adjuvant chemotherapy ($p < .01$), and they were more likely to reject these treatments when offered ($p = .01$). These patients generally did wish to be fully informed and to participate in treatment decisions but the most common reason given for not selecting chemotherapy were the physicians' recommendations ⁷⁰. In another study, in which patients over 70 were given treatment options, 75% chose breast conserving surgery

with radiation and tamoxifen, and only 20% of these reported moderate or severe side effects from the radiotherapy ⁷¹.

2.2.2

Marital Status

Currently married persons live longer, with lower mortality from almost every major cause of death. In a large study of 25,706 persons with any type of epithelial cancer diagnosed between 1969 and 1982 in New Mexico, not currently married cases were more likely to be diagnosed at a later stage, more likely to be untreated controlling for stage, and more likely to have a poorer survival controlling for stage and treatment ⁷². Another American study showed a positive influence of the married state on the decision to pursue axillary lymph node dissection, controlling for age, education, income, insurance (health maintenance organization membership), history of breast or other cancer, extent of comorbid disease, tumor size, vessel invasion, grade, type of surgery, and hormone receptor status. The same study showed a greater likelihood of currently married women to receive either hormonal or chemotherapy (odds ratio 2.97, confidence intervals 1.13 - 7.78) ⁶⁶. Other investigators have also commented on the differences in treatment between currently married and not married cases ⁶⁹,

⁷³

2.2.3

Location

Studies have documented differences in treatment and investigation for breast cancer between different locations. Although some studies have shown that distance from

treatment center and availability of radiation therapy equipment makes a difference in treatment ⁷⁴, others have shown that geographic location and distance from treatment centers do not appear to be the prime cause of differences in treatment.

In an important study of geographic variation in treatment, Farrow ⁷⁵ demonstrated significant variation in the use of breast conserving surgery and radiation therapy post breast conserving surgery, between nine regions of the United States, all of the regions being National Cancer Institute Surveillance, Epidemiology, and End Results registries. Between 1983 and 1986, the areas maintained their relative rankings in the frequency of breast conserving surgery. These wide regional variations could not be attributed to simple patient or physician differences but were regional in scope.

Hospital affiliation with a university or medical school as a teaching institution has positive effects on both treatment and survival indices ^{76, 77}. Hospital involvement in clinical trials has the same positive effect ⁷⁸. Just living in a University hospital district with available radiotherapy improved survival odds while only having the available radiotherapy without being in a university hospital district did not improve the odds ⁷⁹.

Surgeon caseload and surgeon specialization in breast cancer has a positive outcome for treatment and survival ^{78, 80, 81}. The significant variation in use of radiation therapy across geographic areas is found to disappear when control was made for factors related to surgeon workload and specialization in breast cancer. Those surgeons with a larger volume of breast cancer cases and those indicating a special interest in breast cancer are more likely to refer for radiation therapy ^{82, 83}.

Organizational factors including the presence of a multidisciplinary cancer treatment center or dedicated breast cancer centers leads to improved survival ^{74, 84, 85}.

2.3 Problems with Breast Cancer Research

There is a lack of definitive evidence about the appropriate investigation and proper treatment of the older woman with breast cancer. The role of chemotherapy, radiation therapy after breast conserving surgery, and axillary node dissection on the outcome of breast cancer for older women is not yet understood. Perceived scientific uncertainty and lack of policy leads to a wide variation in practice⁸⁶. In a review of the literature up to 1993, it was noted that advances in treatment of breast cancer have not been translated into better health outcomes for women older than 65⁶⁹.

Research into the best treatment for cancer is hampered by the fact that patients' comorbidity status is not taken into account in the routine coding of cancer cases on cancer registries. Comorbidity has a definite effect on survival⁸⁷⁻⁸⁹, but this important information is not available in cancer registry databases. It is not known which comorbid diseases or whether the sheer number of comorbid diseases increase an individual's risk. It has been shown that cancer registrars can code comorbidity both accurately and quickly⁸⁸. It would be useful to determine if cancer registries could routinely code comorbidity without losing any of their present accuracy.

A significant number of cases are not staged. This presents a problem in research as stage at presentation is the most important indicator of outcome⁸⁸. Studies of breast cancer often drop those patients that are not staged. The studies here cited are but examples of many^{78,90}. There is room for cancer registries to partially fill this gap for patients entering cancer treatment centers. Cancer registrars are well trained and know how to read and accurately interpret a chart.

2.4 Key Studies

Key studies were those with excellent and sometimes innovative design. They were chosen because of their methodology. They were often cited in other studies.

Greenfield's ⁶³ study, using the unique method of 'Criteria Mapping' to control for functional status and comorbidity, very effectively showed that it is chronological age that accounts for less than standard treatment of older breast cancer patients. Most subsequent authors addressing co-morbidity have cited his study.

A key study in the Canadian milieu, which is different than the American, was that of Hebert-Croteau ⁶⁴. Using multivariate analysis to control for the effects of comorbidity, disease, hospital, and physician factors, this study showed the effect of age on referral and treatment practices.

Yancik's study, which showed the influence of age on unknown stage, axillary lymph node dissection, breast conserving surgery, and radiation therapy after breast conserving surgery, controlling for comorbidity and stage in a multivariate analysis, was key because it uses the quality assured databases within six SEER (Surveillance Epidemiology and End Results - part of National Cancer Institute in the United States) affiliated cancer registries ⁸.

Goodwin's study, showing the effect of marital status on stage at diagnosis, treatment, and survival of several cancers including breast cancer, was key because of its size, the use of a Surveillance Epidemiology and End Results participating cancer registry, and because of its use of multivariate analysis to control for competing effects ⁷².

Farrow's study of geographic variation in treatment across the United States was key because of its large size (20,000 women) and its use of cancer data from the nine National Cancer Institute Surveillance, Epidemiology, and End Results registries. ⁷⁵

The clinical practice guidelines were key references. These were formulated as a guide for physicians in the practice of evidence based medicine. Best practice alternatives are exhaustively and critically researched from the world medical literature, and presented in an easily interpreted form. The Canadian clinical practice guidelines for the management of breast cancer were published in 1998 but available in 1997. They form the standard to inform treatment practices. The Australian clinical practice guidelines were also considered key. The recommendations in both sets are very similar, however the Australian guidelines give a measure of the level of evidence on which their guidelines are based. In addition, they were published in 1995 and so were certainly available although they may not have been sought by physicians in Canada ⁴¹.

The last key study was the early breast cancer trialist's meta-analysis of the effects of both hormone therapy and chemotherapy on survival ⁵². A meta-analysis, bringing together the results of many randomized controlled trials, is considered to be the highest level of evidence in delineating clinical practice guidelines. For this reason, it must be considered key.

2.5 Conclusion

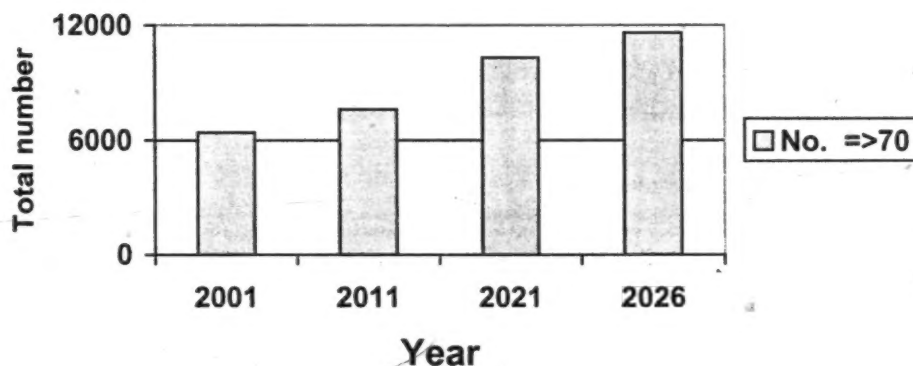
A review of the literature reveals that the improvements made in treatment and improved survival of most patients have not benefited all. The old and patients served in locations with non-specialized staff, non-teaching and non-research hospitals do not attain those benefits. This is due to differences on several levels including individual practice patterns and organizational factors within hospitals and regions. In addition, there are gaps in knowledge about some patient groups, especially the elderly. There is probably room for improvement in the cancer registry database.

Table 2.1 Projected Trends in Absolute and Relative Increase in Females 70 and Over in Canada, 2001 -2026 ^{57, 58}

Year	2001	2011	^a 2021	2026
Females in Canada	15,653,400	16,850,200	17,850,400	18,250,900
Total ≥70	1,665,800	1,964,500	2,676,000	3,009,600
% ≥70	10.6%	11.7%	15.0%	16.5%
Total # Cases in Female≥≥≥70	6,430	7,583	10,329	11,617
Rate=386/100,000				

Figure 2.1 Projected Numbers of Women ≥70 with Breast Cancer For Years 2001-26

Total Number of Women Greater Than or Equal to 70 with Breast Cancer



Chapter 3 - Materials and Methods

3.0 Introduction

This chapter outlines the type of study, data sources for the study, the selection of participants, the selection of variables, and the statistical methods used to analyze the data.

A retrospective cohort study of all Alberta women diagnosed with breast cancer in 1997 was undertaken to determine if certain subgroups of women were less likely to be referred to a specialized cancer treatment center. The study identified cases through the use of one database, the Alberta cancer registry, and subsequently identified whether those cases had an appointment at a specialized cancer center through the use of another separate database, AXON. The two databases were merged on the basis of the common Alberta Cancer Board number and appropriate variables were drawn from the combined database. Statistical analyses included multivariate analysis to identify significant factors for no appointment, and survival analysis to identify whether no appointment was associated with poorer survival.

3.1 Data Sources

3.1.1 Alberta Cancer Registry

The Alberta Cancer Registry formed the initial data source from which information was collected for every case of female breast cancer in the province for 1997. According to the 1993 publication, 'The Making of the Canadian Cancer Registry', cancers were first registered in Alberta in the early 1940's for payment purposes. By

the mid 1960's registration was recognized as a valuable tool for cancer surveillance and research. Therefore, legislation, the Alberta Cancer Programs Act, was enacted to ensure that all reports of cancer (surgical, pathological, cytological, and clinical), are submitted to the Alberta Cancer Registry for surveillance purposes⁹¹. Therefore, all cases of cancer in the province should have a report in the registry. If the patient reports to a cancer center as an inpatient or outpatient, then a patient chart is made. If the patient is non-reporting, then the information about that patient stays within the cancer registry as a report. In either case, patients are given a unique, patient specific, Alberta Cancer Board number, if they do not already have one from a previous cancer.

In addition to information pertaining to live patients, the registry collects information from death certificates. Few cases are reported by death certificate only. The 1996 'Canadian Cancer Incidence Atlas' reports that microscopic confirmation of breast cancer, that is, from living patients, is obtained in over 98% of cases in Alberta. Regular linkage from the registry to the Department of Vital statistics provides data about malignancies that are found on autopsy or described by death certificate only, amounting to 2% of breast cancer cases⁹². Theoretically, therefore, the registry should contain information on every case of breast cancer in the province.

Information on every case is filed through the Axon system, the Alberta Extensible Oncology Network, a province wide, electronic database. Every case is assigned a number. Additional information concerning the cancer is requested by the registry on a form sent back to the physician⁹¹. Appendix I gives an example of the letter and form sent back to physicians from the Alberta Cancer Registry. This form, in addition to seeking additional information about the cancer, invites a referral by the physician to an Alberta Cancer Board cancer facility. Other than this one follow-up letter to the notice of a malignancy, the Alberta Cancer Registry does not follow up on patients not referred. Deaths are captured through the linkage to vital statistics.

The form in which patient files are kept varies, based on whether the patient is actually referred to an Alberta Cancer Board facility. The first notification of the cancer is kept as a report. If the patient is subsequently referred to a facility by the physician, a chart is created. The fact that some patients only have a report was an indication that not all cases of breast cancer were referred to an Alberta Cancer Board facility.

3.1.1.2 Data Quality

Quality is a property of the information stored in the registry database and is highly dependant on the techniques that are used to create the database⁹³. Quality depends on the completeness of coverage for a cancer, completeness of information for each variable, and accuracy of information. Completeness of coverage is frequently specified by the relative frequency of cases ascertained by death certificate only. For breast cancer, with only 2% ascertained by death certificate only, coverage is considered very high. Completeness of the information is defined as the frequency with which information is available on a specific variable. Although completeness of information cannot be maintained on all variables, a certain core set of variables is considered essential. Complete information is sought by the registry for these core variables. Accuracy is the notion that the information in the registry should reflect the actual situation⁹³.

In Alberta, quality is maintained using routine checks and occasional quality assurance checks such as the report by Berkel. Some of the routine checks include automatic checks, for instance, flags if sex specific cancers do not occur in the appropriate sex, or flags ensuring that the topographical site and the histology match⁹². Indicators of quality include the percentage of cases that are microscopically confirmed, the fraction coded to other or unspecified sites and, within site, to unspecified morphology. In Alberta, 98% of breast cancers are microscopically

confirmed, and 98% have a specific morphology⁹². Because of the high level of microscopic confirmation and known morphology, the quality of breast cancer data in the registry is considered high.

Within the registry, information is collected from charts and reports by specially trained technicians (coders). The data is coded into standardized fields within an electronic database. For core fields, registry staff pursue information from outside sources such as hospitals, physicians, and Statistics Canada, if necessary.

Coders are extensively trained and then continually upgraded through inservice, conferences, and telecommunications. The registry itself must be re-certified regularly by both national, the Canadian Council of Central Cancer Registries, and international agencies, the North American Association of Central Cancer Registries (NAACCR). The standards are based on the quality indicators that were outlined. NAACCR sets the 'gold standard' in excellence. The Alberta Cancer Registry has been awarded the NAACCR gold certification for all the years that certification has been in place.

Core information that the registry collects includes sex, date of birth, date of diagnosis, date of death, location of residence, marital status, ICD-O (international classification of diseases - oncology) morphology, ICD-O topography, tumour behavior, clinical and pathological stage (if available), ICD-O grade (if available), treatment, and previous malignancies. The routine linkage of the registry to vital statistics captures deaths occurring outside the time of attendance at a cancer facility. The registry routinely rechecks death certificate 'cause of death' against the chart and may reclassify the cause of death within its own database. If the chart check reveals that the cancer was still active at the time of death, the registry will code the cancer as the cause of death.

Because of the internationally high standards that are maintained, the extensive training for staff, and the automatic checks that are in place, and the quality assurance initiatives, the registry data can be trusted for accuracy and completeness. This accurate, complete, and coded data is available to authorized staff for research and surveillance within computer programs that can handle both large volumes of data and the statistical procedures necessary for analysis. SAS software is the program used by Alberta Cancer Board staff. SAS was used for this analysis.

3.1.2 Appointment Data

Appointments to a specialized cancer center for any procedure or consultation are handled by the admissions department or outpatients, who enter the appointment data into Axon, the Alberta Extensible Oncology Network, described previously as the province wide electronic oncology database. The Alberta Extensible Oncology Network has been in operation since 1990. Since 1991, it has covered the whole province. By 1997, the time of the study, the author was assured that no appointments should have been missed by the system. Axon is used by the admissions department and outpatient clinics to schedule appointments. Only people in these departments who are authorized may book appointments or change the status of appointments. Axon is also used by the cancer registry to record data about the cancer. Only registry staff have access to the registry database. Staff in registry cannot book or change appointments, while staff in admitting do not code the cancer for the registry. So although the same system is used for recording both data sets, because of the access issues, they do form two databases. These were the sources of information for this study.

Every appointment is characterized by the person specific Alberta Cancer Board number, year, month, day, time, appointment type, appointment status, department, procedure, ordering doctor, and scheduled event. Patients not referred to a

cancerboard facility will not have appointment information but they will still be in the Axon system as the information about their cancer has been entered by the Alberta Cancer registry.

Patients who are referred will have an appointment that should be characterized by an appointment status that is either scheduled, arrived, show, no-show, cancelled, no further follow-up, or chart check. Chart check is for patients that do not come to the cancer center but an appointment to check their chart is scheduled so that planning regarding their particular case can be made. This often is scheduled at the end of treatment to ensure that the patient needs no further treatment. No further follow-up is the appointment type made for patients discharged from care. No further follow-up automatically appears once a notice of death has been entered into Axon and all further follow-ups are automatically cancelled. If no further follow-up is entered for a live patient, all follow-ups will be cancelled.

If an appointment is made for a patient to attend, than the appointment status is 'scheduled' and the appointment type should be 'firm'. As soon as the patient presents at the admissions desk and an appointment slip is given to the patient, the appointment status changes automatically to 'arrived' within the Axon system. Because this information is immediately available within Axon, all staff needing to know the whereabouts of a patient can access that information and not have to burden the admissions department with questions as to whether their patient is in. The appointment status 'arrived' changes automatically to 'show', within 2 days of the appointment date, so that the status of that particular appointment will be permanently recorded as 'show'. If a patient misses the appointment, then the appointment status is changed from 'scheduled' to 'no show' or 'cancelled'. Therefore, patients with appointments at a cancer facility should have an appointment status of either 'show', 'cancelled', 'no-show', 'no further follow-up', or 'chart check'. The variations in appointment status assist both admissions and medical staff in knowing if the patient is expected at the facility and if she has arrived.

The appointments database not only facilitates information, it allows for quality assurance checks. Individual patients are not as likely to fall through the cracks. If they have had an appointment made and they did not show for the appointment, then the appointment status of no show or cancel can trip the system to reschedule the patient or at least take note that the patient did not come. Those who had a clinical chart check should likely have an automatically rescheduled further appointment unless there is no need for further follow-up, which is then recorded in the appointment status.

3.2 Participant Selection

The cohort consisted of all women diagnosed with a first breast cancer in 1997, resident in Alberta at the time of diagnosis. Breast cancer is initially identified by the topography code within the Alberta Cancer Registry. The topography code identifies the part of the body where a cancer is located. For a cancer of the breast, the topography code will be C50. Other types of cancers that may be located on the breast but are not breast cancers include lymphomas and nevi. These are excluded using the morphology code for lymphomas ($M \geq 959$ and ≤ 994 , ie morphology) and nevi ($M \geq 872$ and ≤ 879). The morphology code describes the type of cells that are cancerous. Both the morphology and topography codes used by the Alberta cancer registry were based on the second edition of the International Classification of Diseases for Oncology⁹⁴. Residence in Alberta was determined from the postal code, first letter T, or the standard geographic code (9909). Year of diagnosis is calculated from data within the cancer registry on date of diagnosis.

Once cases with a breast cancer in 1997 were identified, those cases having had a previous invasive cancer prior to the breast cancer, and those cases who died within 90 days of diagnosis were excluded. Cases with only a previous non-melanoma skin cancer (NMSC) or in-situ cancer were not excluded. Cases with a previous invasive

cancer could have survival affected by the previous cancer and appointments may not have been for the 1997 breast cancer. Cases that died within 90 days of diagnosis may have been too advanced to benefit from an appointment.

Figure 3.1 shows selection of participants for this study. Of 1,564 incident cases of female breast cancer diagnosed in Alberta in 1997, 142 were excluded because of a previous invasive cancer, and 32 were excluded because of death occurring within 90 days of diagnosis. One further case was excluded because the tumour morphology was 'hemangioma' which is distinct from the breast cancers being studied. Therefore, 1389 cases were left within the study.

3.3 Data Merger

Both the appointment and the registry data sets were filed according to the patient specific Alberta Cancer Board number (ACB no.). Both data sets were entered using the Axon system, however, they are maintained as two separate sets of information. Using the unique identifier, the ACB no., the 'appointments' and the 'registry' data were merged.

The method of combination of the data sets for this study was developed with the assistance of the Alberta Cancer Board provincial programmer. The final data set was composed of the first appointment after diagnosis of breast cancer, the time between diagnosis and appointment, plus the registry data on the person, malignancy, treatment, and vital status.

Using both data sets, it should be possible to ascertain variables and to determine which breast cancer patients did or did not have an appointment. Patients listed on the registry but not on the admissions data set have not had an appointment. For

those listed on both databases, the timeliness and type of appointment could be determined.

The merged registry and appointment data contained the variables for each patient. Study variables that were chosen or calculated included demographic variables, such as age, sex, location of residence and marital status; disease variables including topography, morphology, behaviour, stage, and grade of the cancer; treatment variables including type of surgery, radiation therapy, and hormone or chemotherapy; and finally, vital status including cause and date of death, if applicable. In addition, patients were categorized into groups depending on whether their appointment status was a timely appointment, no appointment, or late appointment.

3.4 Group Designation

Three groups of patients were identified based on whether or not they had had an appointment and if this appointment was timely. A timely appointment was one within 90 days of diagnosis. This is based on the Canadian clinical practice guidelines for radiation therapy for breast cancer, which indicate that radiation therapy should be started within three months of diagnosis⁴⁴. The only exception to this would be those cases in which chemotherapy is given first, in which case the chemotherapy should have been started within three months of diagnosis. Either way the appointment would have been within three months of diagnosis.

The three groups of patients consisted of those having a timely appointment within 90 days of diagnosis, those not having an appointment, and those having an appointment after 90 days from diagnosis.

Table 3.2 depicts group status and time from appointment.

Of the 1389 cases in the cohort, 1187 (85.5%) had their appointment 90 days or less from diagnosis and these cases formed the timely appointment group. They were the reference group against which the other groups could be compared. 119 (8.5%) cases had no appointment and were the no appointment group. The timely appointment and the no appointment formed the two primary groups for statistical analysis.

83 (6%) of the cases had appointments more than 90 days from diagnoses. These were the late appointment group. They did not, by definition, fit into the timely appointment group but they did have an appointment, so neither did they fit into the no appointment group. 36 (43%) of these had an appointment within the fourth month, 13 (16%) had an appointment within the fifth or sixth month, 20 (24%) had an appointment 6-12 months after diagnosis, and 14 (17%) had appointments over a year from the original diagnosis. These 83 cases were analyzed as a measure of robustness for the study, after the primary appointment and no appointment groups had been analyzed. Robustness means that we can draw the proper conclusions even when all our assumptions are not met⁹⁵. In these cases, neither the criteria of referral within 90 days of diagnosis nor the criteria of non-referral were fulfilled. Therefore, these cases did not satisfy all of the assumptions. The test of robustness is to see whether their inclusion has significant effect on the analysis.

3.5 Statistical Analysis

3.5.1 Variable Selection

Variables were chosen for inclusion in the model during study planning based on clinical suspicion or review of the literature. Control variables such as age, stage, and grade were also chosen. These are known to influence survival. Variables were chosen for which there was usually data available. In spite of this, there is still some

missing data, particularly in stage and sometimes in grade. In order not to lose study subjects, unknown data was given a code. Special interest variables included the location of residence and marital status.

Age in completed years was calculated as the date of diagnosis minus date of birth at the time of diagnosis. Age was then categorized into a trichotomous variable (<50, 50 - 69, ≥ 70). Under 50 was the reference group. Age categories reflect treatment categories referred to in the Clinical Practice Guidelines⁵¹. A dichotomous age variable was also calculated (<70, ≥ 70). <70 was the reference group.

Table 3.3 lists of age, marital status, and location variables.

Marital status had six categories within the registry. It was scaled down into a dichotomous variable for this study. Currently married included common-law and married, and formed the reference. Not currently married included single, widowed, divorced, and separated.

Residence was calculated by regional health authority. The province of Alberta is comprised of 17 regional health authorities. Regional health authorities are responsible for hospitals, continuing care facilities, community health services, and public health programs. They deliver health services in the region and work with local communities to deliver health services to local residents.

Figure 3.2 shows the composition of the five location categories based on regional health authorities.

A five category location variable was constructed based on the 17 regional health authorities. The two major urban, regional health authority's were Calgary (Calgary regional health authority 4) and Edmonton (Capital regional health authority 10). The rest of the province was divided into Southern Alberta (containing regional health authority's 1, 2, 3, & 5), Central Alberta (containing regional health authority's 6, 7, 8, & 9), and Northern Alberta (containing regional health authority's 11, 12, 13,

14, 15, 16, & 17). Calgary was the reference category because it had the highest percentage of cases with appointments.

Location was also categorized as rural or urban by postal code. Rural postal codes are always 'T0'. Rural means living on a farm or place outside of city, town, village, and hamlet. Urban is any community settlement that is not rural. Urban postal codes are 'T1-9' but not 'T0'. Urban was the reference category.

Table 3.4 lists important disease variables.

Disease variables included 'International Classification of Diseases for Oncology' (ICD-O) classifications for morphology and grade. The ICD-O morphology was a dichotomous variable with usual morphology including either ductal or lobular cancer or unusual morphology which included all other cancer types. The reference morphology was usual. Grade was a trichotomous variable of low grade (grades I and II), high grade (grades III and IV), and unknown grade. Low grade, the reference grade, has a better prognosis than high grade.

Appendix II shows summary of AJCC breast stages.

Cancer stage was based on the American Joint Committee on Cancer (AJCC) staging system. The system is based on the extent of cancer at the tumour site and its spread to nodes and metastases. The tumour, node, metastases system is most often referred to as the TNM system. Stage groupings for tumours of the breast are the same for the AJCC and the Union Internationale Contre le Cancer (UICC) ⁴². Stage was calculated as a trichotomous variable. Low stage refers to stages I and II, which includes tumours ≤ 5 cm, with or without movable axillary lymph nodes, and without metastases. High stage refers to Stages III and IV and includes tumours > 5 cm, with or without movable or fixed nodes, and with or without metastases. Unknown stage referred to cases in which staging information was unavailable. Low stage formed the reference category.

Variables not available from the cancer registry included comorbidity and estrogen/progesterone receptor status.

See Tables 3.5 and 3.6 for treatment and vital status variables.

Treatment variables included a dichotomous variable for treatment with chemotherapy and/or radiation therapy. Hormone therapy is not included in this dichotomous treatment variable because hormone treatment does not require referral to an oncologist. The dichotomous variable for chemotherapy and/or radiation therapy demonstrates treatment arising from a referral to an oncologist whereas hormone treatment may not. If the patient had either or both chemotherapy and/or radiation therapy than the treatment group was regarded as yes, the reference category. No treatment by either of these modes formed the test category. Radiation therapy is local treatment, while chemotherapy is systemic treatment.

There were also dichotomous variables for each of these treatments individually. The reference value was for those who had had the treatment, either chemotherapy, radiation therapy, or hormone therapy while the test category was for those that did not receive the treatment. It is important to note that some patients in the 'no appointment' group were known to have received tamoxifen. Therefore, they were treated for systemic disease even if they did not have an appointment.

There were also dichotomous variables for surgery and type of surgery. Having surgery formed the reference group for the surgery variable, while no surgery would be the test category. Breast conserving surgery formed the reference group for the surgery type variable and mastectomy formed the test category. Again, it is important to note that most patients in the 'no appointment' group did receive surgical treatment.

There were two treatment variables for local and systemic treatment. Standard local treatment is either mastectomy or breast conserving surgery plus radiotherapy. This is the reference for the local treatment variable. Local treatment that was outside the

standard was the test variable. It is noted, that patients defined as "not standard" local treatment include not only patients who received breast conserving surgery without radiation therapy, but also those who had no surgery at all. The lack of surgery in such cases may or may not have been appropriate, depending on advanced stage of disease, co-morbidities, patient choice, and other factors. Systemic treatment is either chemotherapy or hormonal therapy. The reference was to receive either of these treatments while the test was not to receive either. Neither of these variables are necessarily dependent on a referral. Patients can have standard local treatment and systemic hormone treatment without being referred to a cancer specialist. Having these variables is important in categorizing the kind of treatments that different groups of cases received.

Vital status, as listed in the registry, was available as alive, dead, or not confirmed. Not confirmed meant that the patient was dead but that the chart or report had not yet been finally coded. At the time of death, the cause of death is checked and the chart is scrutinized for other primary cancers that may not have been coded within the cancer registry database. Any mistakes are corrected. For the thesis, vital status is listed only as dead or alive, there being no reason to include a third category.

The survival time was calculated using date of diagnosis, and either the death date or a cut-off date for censored values. Censored values are for those cases who haven't died and for cases that have died, but not from breast cancer. Their survival time is used up until the study cut off date, (Sept. 30, 2001) or the date of death if they had died before that. Cause of death was dichotomized to either breast cancer or any other cause.

3.5.2 *Descriptive and Univariate Analyses*

Mean age and age group composition were established for each of the outcome groups, timely appointment, no appointment, and late appointment. For each of the outcome groups, cross tabulations of the variables with age group were run to compare differences between age groups within an outcome group. Chi square analysis was used to reveal significant differences between the age groups. Univariate logistic regression analysis of each variable was run with appointment group status as the outcome. The univariate analysis was done to determine which variables might be significant to a multivariate logistic regression analysis with appointment group as the outcome.

After the initial univariate logistics regressions (which used only the timely and the no-appointment groups), the late appointment group was added to each of the other two groups, in turn, as a test of robustness of the model. The question was whether the addition of this group to either of the two main groups would make any difference to the final results.

3.5.3 *Logistic Regression*

Logistic regression was the multivariate procedure of choice to test the effect of variables on the dichotomous outcome, timely appointment group or no appointment group. Logistic regression fits the dichotomous outcome. Independent variables may be either dichotomous, interval or continuous. The likelihood that the exposure variables have a significant effect is tested by the likelihood ratio test, and the Wald test. The likelihood ratio test, a test of the difference in the log likelihood statistic (-2LL) between two models, one containing a variable and the other not, is taken as the most accurate test by statisticians⁹⁶. The likelihood ratio is approximately distributed as chi-square with degrees of freedom equal to the number of parameters (or B's) set

equal to 0 in the null hypothesis. The logistic regression procedure determines an odds ratio estimate with confidence intervals and p-values for all independent variables entered into the model. Therefore, it can be determined if there is a significant odds that a variable is associated with the no appointment group. Further, the odds for any one variable is adjusted for all other variables contained within the model.

All variables that were significant at the $p \leq 0.20$ level in a univariate regression were entered purposively into a multivariate logistic regression model. The purposive entry of variables was cross-checked using an automatic forward stepwise approach. The automatic forward stepwise approach provides information on the statistical strength of specific variables because of the likelihood ratio. The variable with the highest likelihood ratio statistic is the one first chosen to be entered into the stepwise procedure. One can see the likelihood ratio statistic decreasing as successive variables are entered until the variables finally become statistically insignificant.

Other criterion for entry into the model was lack of evidence for high collinearity both between the independent variables themselves, or between the independent and the outcome variable. This was checked outside the model by cross tabulations.

Confounding variables have effects which cannot be distinguished from those of the variable being studied². Therefore, unless it is possible to adjust for confounding, bias can occur. Confounding variables should be included in a model if they can be identified and if they are available.

Interaction is a property exhibited by some variables. The effect of one variable differs depending on the level of another variable². Interaction factors are also called effect modifiers or product terms. Interaction factors are constructed as the product of two variables. They must be tested for significance in the model and kept as part of

the model if they are significant. They can be removed if not significant, a sign of no interaction.

Interaction variables were constructed from combining each of the variables in the final model with each other as product terms. They were added to the final model one at a time. Of particular interest would be interaction between location and either age or marital status. Significance in any of the interaction variables would be shown by a significant difference in the likelihood ratio between the final model and the final model with the added interaction variable. More simply, significance of an interaction variable would also be shown by the p-value. Any interaction variable that is significant must be kept in the model as must its component variables ⁹⁶.

A goodness of fit test determines whether the sample data are in conformity with the hypothesized distribution ⁹⁷. The measure of fit used in this analysis was the Hosmer and Lemeshow C statistic. This is a measure of the conformity of observed values in the model to expected values when the data are ordered into deciles. When $Y=1$ (the outcome of being in the no appointment group), the expected values are 'obtained by summing the estimated probabilities over all subjects in a group'. When $Y=0$ (not the outcome in question), the 'estimated expected value is obtained by summing, over all subjects in the group, one minus the estimated probability' ⁹⁸. The C statistic is obtained from calculation of the Pearson chi-square statistic from the table of observed and estimated frequencies. A high p-value ($>.05$) from the calculation indicates a good model fit.

The model was tested for robustness by the addition of the 83 late cases, first as part of the appointment group and then as part of the no appointment group. If the model is robust, then the addition of these 83 cases will not make much difference to the outcome, no matter to which side they are added.

3.5.4 Survival

Survival was a second outcome for this study. Do the characteristics that influence appointment group status also influence survival? Does appointment group status itself affect survival?

Survival is time until an event (failure) occurs⁹⁹. In the context of this thesis, survival time is measured from the date of diagnosis of breast cancer until the date of death from breast cancer. Most cases have not died, so that exact survival time is not known. In these cases, censoring measures their contribution to the survival outcome⁹⁹. Censoring measured the time from diagnosis of breast cancer until September 30, 2001, a predetermined cutoff time. Cases that did not die from breast cancer were also censored, their contribution to the survival being measured from date of diagnosis of breast cancer until date of death.

Cause of death given is the registry cause of death which is checked by the registry prior to final coding of a chart. Therefore, the cause of death data is likely quite accurate. Even death certificate cause of death for breast cancer has been found quite accurate¹⁰⁰. Accuracy on death certificates is highest for malignancies and among malignancies, breast cancer has the highest accuracy. Breast cancer tends to be overreported on death certificates, a situation that is corrected on the registry database.

Survival was tested in two ways, by the Kaplan-Meier analysis and by Cox regression^{101, 102}. The Kaplan-Meier analysis provides a survival curve and a test of significance for the variable being tested. This test of significance is the 'log rank statistic', a large sample chi-square test⁹⁹. If the $p \leq 0.05$, then it can be assumed that the survival of the two cohorts is significantly different. The Kaplan-Meier analysis also provides log minus log curves from which to test the proportional hazards assumption on which the Cox survival analysis is based. The proportional hazards assumption is that the effect of a variable on survival is constant over time.

All variables that satisfy the proportional hazards assumption can be included in the Cox regression. Each variable is adjusted (controlled) for the effects of all other variables included within the model. The test variables from the logistic regression, age, location, and marital status were entered in the model. In addition, the control variables stage, grade, and morphology were entered. Importantly, to address the question regarding survival of appointment groups, appointment group status was included in the Cox regression.

The Cox regression provides a hazard ratio and confidence interval for each variable in the model. The hazard ratio gives the increased (or decreased) likelihood of death from breast cancer (the outcome here) that a person with a particular characteristic faces. If the confidence intervals do not include one, then the hazard ratio is significant.

Some variables that had been significant in the Kaplan-Meier Analysis may not be significant in the Cox regression because of the control provided by this multivariate model. Cox regression is considered a robust method of survival analysis that does not require an underlying hazard but gives a model very similar to the exact parametric model.

The Cox regression was accomplished using both a purposive variable entry and an automatic forward stepwise introduction of variables to check the first approach. Variables entered into the multivariate Cox regression analysis were chosen first by their significance ($p \leq 0.20$) on the Kaplan-Meier analysis and in univariate Cox procedure. As in the logistic regression, the investigator wants to control the model, but the automatic forward stepwise approach provides both a model check and data about the importance of different variables.

As a measure of robustness of the survival model, the 83 late cases were added to the final Cox regression model, first as part of the appointment group and then as part of the no appointment group. If the model is robust, then the addition of these 83 cases will not make much difference to the outcome, no matter to which side they are added.

Figure 3.1: Criteria for Inclusion or Exclusion from Study

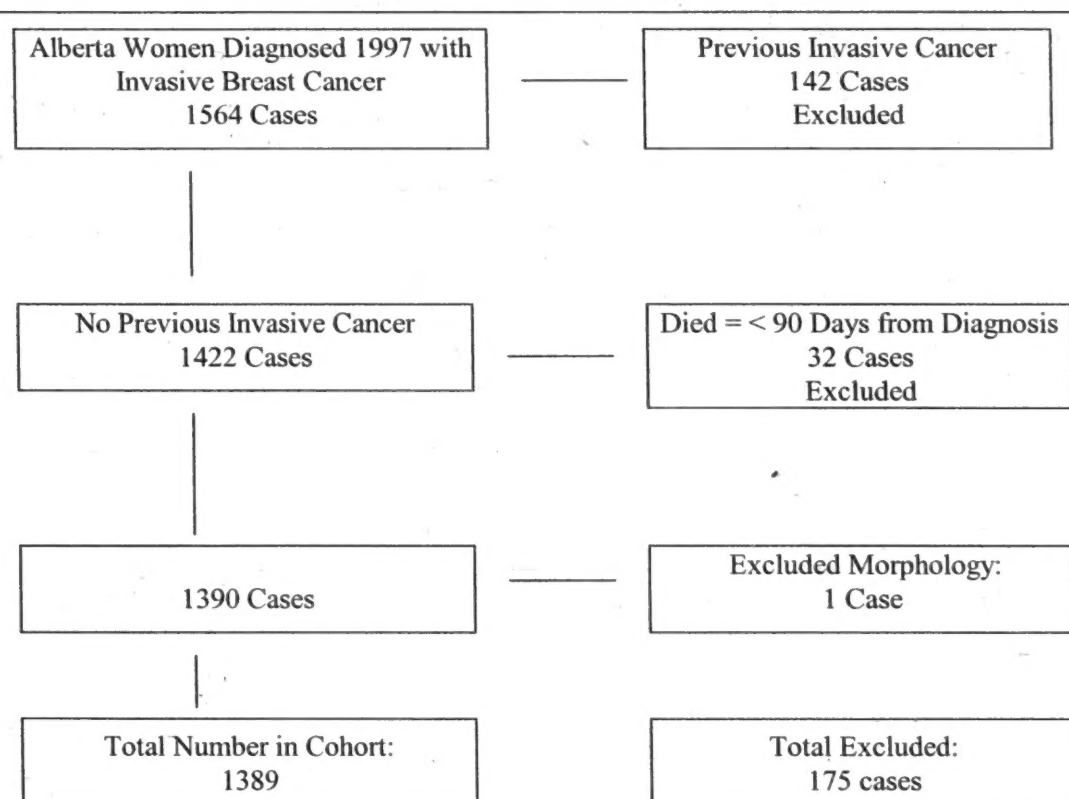


Table 3.1: Appointment Groups.

Appointment Status and Time from Diagnosis to Appointment	Number of Cases
Timely Appointment within 90 days diagnosis	1187
No Appointment	119
Appointment > 90 days diagnosis	83
Total:	1389

Table 3.2: Time from Diagnosis to First Appointment.

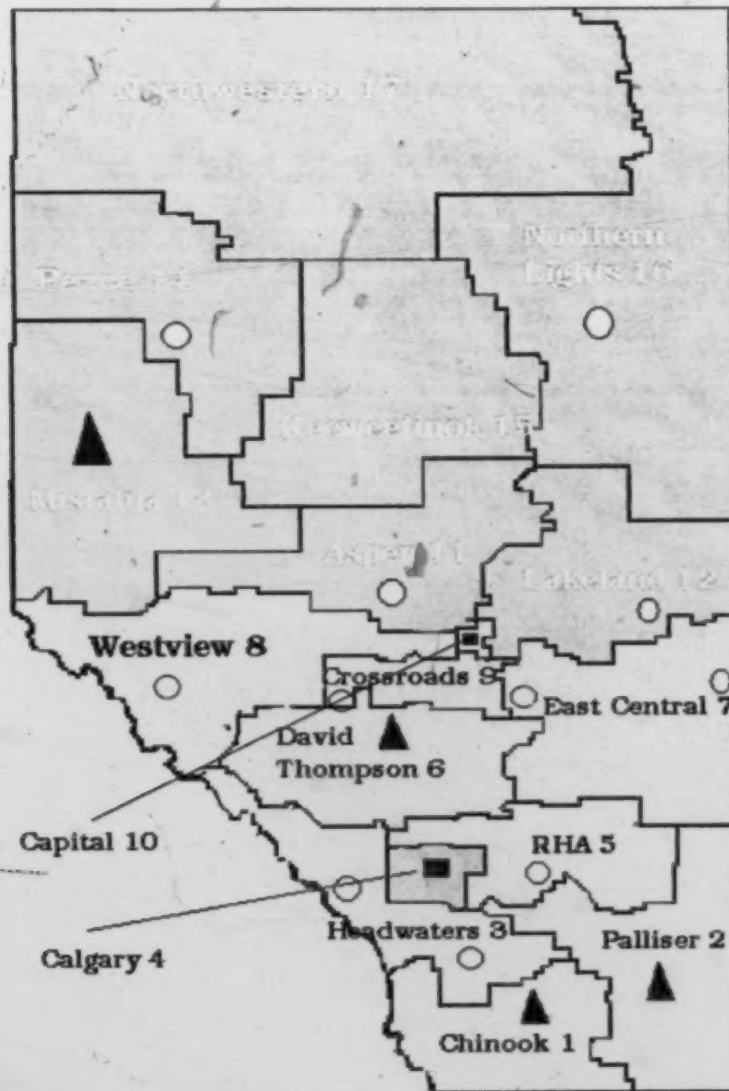
Group	Time from Diagnosis to Appointment	# Cases	Total (%)
Timely Appointment:	<90 days	1187	1187 (85.5%)
No Appointment		119	119 (8.5%)
Late Appointment	≥90 days		
	>90<120	36	
	>120<180	13	
	>180<365	20	
	>365	14	83 (6%)
Total:			1389

Table 3.3: Description of the Demographic and Location Variables.

<i>Var. Name</i>	<i>Description</i>	<i>#</i>	<i>Category Values</i>
		<i>Categ's</i>	
ACB No.	Individual Patient Number		
<i>Demographic Variables</i>			
Age Group	Trichotomous Age Group	3	0 = <50* 1 = 50-69 2 = ≥70
Age Group	Dichotomous Age Group		0 <70 1 ≥70
Marital Status	Dichotomous Marital Status	2	0 = married or common law 1 = single, separated, divorced, or widowed
<i>Location Variables</i>			
Location	5 Category Location Based on RHA of Residence at Diagnosis	5	0 = Calgary (RHA4) 1 = Edmonton (RHA10) 2 = Southern Alberta (RHA's 1,2,3,&5) 3 = Central Alberta (RHA6-9) 4 = Northern Alberta (RHA's 11-17)

Values of 0 for the variables are the reference values.

Figure 3.2 Map of Alberta showing 17 regional health authorities and their division into five categories for location.



Northern Alberta
= Location 4

Central Alberta
= Location 3

Southern Alberta
= Location 2

Edmonton
(Capital)
= Location 1

Calgary
= Location 0

- Cross Cancer Institute (Edmonton) and Tom Baker Cancer Centre (Calgary)
- ▲ Associate Cancer Centres
- Community Cancer Centres

Table 3.4: Description of the Disease Variables.

Disease Variables

<i>Var. Name</i>	<i>Description</i>	<i># Categories</i>	<i>Category Value</i>
Morphology	ICD-O morphology	2	0 = ductal or lobular (ref *) 1 = all other morph
Grade	ICD-O grade	3	0 = Grades I & II (ref) 1 = Grades III & IV 2 = unknown grade
Stage	Stage	3	0 = Stages I & II (ref) 1 = Stages III & IV 2 = unknown stage

* ref = reference value

Table 3.5: Description of the Treatment Variables.

<i>Treatment Variables</i>			
<i>Var. Name</i>	<i>Description</i>	<i># Categories</i>	<i>Category Value</i>
Treatment group	Either radiation and/or chemotherapy	2	0= yes (reference) 1= no
Chemo-therapy	Chemotherapy	2	0= yes (reference) 1= no
Radiation treatment	Radiation	2	0= yes (reference) 1= no
Hormone treatment	Hormone therapy	2	0= yes (reference) 1= no
Had Surgery	Surgery	2	0= yes (reference) 1= no
Surgery type	Type of surgery	2	0= Breast Conserving 1= Mastectomy
Standard Local Treatment:	Either Mastectomy or Breast Conserving Surgery + Radiation Therapy	2	0= Standard 1= Not Standard
Systemic Treatment:	Either Chemotherapy and/or Hormone Therapy	2	0= Yes 1= No

Table 3.6: Description of Vital Status Variables.

<i>Vital Status Variables</i>			
<i>Var. Name</i>	<i>Description</i>	<i># Categories</i>	<i>Category Value</i>
Censored	Vital Status	2	0 = Alive, or Dead from Other Cause 1 = Dead from Breast Cancer
Survival	Survival Time	Years	Alive = (30,9,01) - date of diagnosis Dead = date of death - date of diagnosis
Death Cause	Cause of Death	2	0 = Other 1 = Breast Cancer

Chapter 4 - Descriptive Characteristics and Univariate Results

4.0 Introduction

This chapter will give a description of each of the appointment groups and describe differences between the age groups within each of the appointment group categories. It will compare the characteristics of the timely appointment group to the no appointment group, and give chi-square probabilities of the likelihood of significant differences between these two groups.

It will describe the results of univariate logistic regression for the significance of single variables to group status. As a measure of robustness, it will also show the changes in the univariate results if the late appointment groups is added as part of either the timely appointment or the no appointment group.

4.1 Descriptive Characteristics of the Breast Cancer Cohort

4.1.1 Group with Appointment ≤ 90 Days

Tables 4.1- 4.5 shows a comparison of the variables discussed below by age group for those with timely appointments. The average age of this group was 57.4 years (SD=13.4), with a range of 80 years from age 15 to age 95. 35% of this group were under 50, 44% were between the ages of 50 and 69, while 21% were 70 or over. 66% of the group were currently married while 34% were in a category including single, widowed, divorced, and separated. As would be expected, there is a marked shift from currently married to other category from the youngest to the oldest age group (chi-square $p < 0.001$).

76% of the group were either stage I or II, 11% were stage III or IV, and 13% were not staged. Nearly twice as many cases in the oldest age group (age 70 or older) were

not staged as compared to the other age groups (chi-square $p=0.003$). 60% were low grades I and II, 29% were high grades III and IV, while 11% were not graded. Significantly more cases in the oldest age group were not graded, while more in the youngest age groups were high grade (chi-square $p<0.001$). Significantly more cases in the oldest age group had an unusual morphology ($p\text{-value} = 0.037$).

As can be seen from the totals on the right side of Table 4.2, approximately 60% of the patients came from the two largest cities, representing Calgary and Edmonton, while the other 40% came from the rest of the province. Specifically, 33% were from the Calgary, 28% were from Edmonton, 13% were from Southern Alberta, 14% were from the Central Alberta, and the remaining 12% were from Northern Alberta. There were significant differences in the age distribution between these five regions. Calgary and Central Alberta had the highest percentage in the youngest age group. Edmonton, Southern, and Northern Alberta had the highest percentages of women in the middle age group, while Southern Alberta had the highest percentage of patients in the oldest age group. 79% of this group were urban (village, town or city) while 21% were rural by postal code. Significantly less women in the youngest age group lived at a rural postal code ($p = .007$). The rural women were most likely to be in the middle age group.

94% received surgery while 6% did not. Those in the oldest age category were significantly less likely to have surgery (chi-square $p=0.003$). Of those who had surgery, 58% had breast-conserving surgery while 42% received more extensive surgical treatment. Of those who had breast-conserving surgery, 83% also received radiotherapy. Of those who had complete breast removal, only 20% had radiotherapy.

There were no significant differences between the age groups regarding the types of surgery but there were significant differences in the percentages receiving radiation after breast conserving surgery. 91% of those in the under fifty age group, 86% in the

50 - 69 age group, but only 60% in the 70 and over age group had radiation therapy following breast conserving surgery (chi-square $p < 0.001$).

Surgery and radiotherapy fall into the category of local treatment for breast cancer. Radiotherapy requires referral to an oncologist. Radiotherapy should usually follow breast conserving surgery but may not be necessary following mastectomy. The above results indicate that the youngest and the middle age groups usually received standard protocols for surgery and radiation, when necessary, while significantly less cases in the oldest age group received the recommended protocol. 91 % of the under 50 age group received either mastectomy or breast conserving surgery plus radiation therapy, both choices considered standard local treatment. 87 % of those fifty to sixty-nine received either form of standard local treatment, while only 70 % of those 70 and over received standard local treatment.

Systemic treatment for occult microscopic metastases takes the form of chemotherapy and/or hormone therapy. Neither treatment is necessary in very early stage breast cancer, although some patients would still prefer treatment.

Chemotherapy requires referral to an oncologist, while hormone therapy does not. Significantly less patients in the oldest age group received any systemic treatment (66%), although a substantial number were treated systemically.

193 (14%) persons in the timely appointment group have died. Of these 73% died of breast cancer. Breast cancer was the cause of death in 95% of the youngest age group, 74% of the middle, and 49% in the oldest age group.

Cases with Appointment Less Than or Equal to Ninety days from Diagnosis

Table 4.1: Cross Tabulations of Marital Status, Stage, Grade, and Morphology within Three Age Groups for the Group with Appointment ≤ 90 Days from Diagnosis (n=1187)

	< 50 (n=409, 34%)	50 - 69 (n=527, 44%)	≥ 70 (n=251, 22%)	Total (n=1187)
Mean of Whole Group				57.4 years
Age Range of Whole Group				15 - 95
Age Group	35 %	44 %	21 %	100 %
Marital Status				
Currently Married	78 %	68 %	42 %	66 %
Other	22 %	32 %	58 %	34 %
Stage				
I & II	76 %	79 %	69 %	76 %
III & IV	13 %	10 %	12 %	11 %
Unknown	11 %	11 %	19 %	13 %
Grade				
I & II	52 %	65 %	64 %	60 %
III & IV	37 %	25 %	22 %	29 %
Unknown	11 %	10 %	14 %	11 %
Morphology				
Ductal or lobular	94 %	92 %	89 %	92 %
Not Ductal or Lobular	6 %	8 %	11 %	8 %

Table 4.2 Cross Tabulation of Five-Category Regional Health Authority Based Location, and Rural/Urban Location for Three Age Groups for the Group with Appointment $\leq$ 90 Days from Diagnosis (n=1187)

	< 50 (n=409, 34%)	50 - 69 (n=527, 44%)	$\geq$ 70 (n=251, 22%)	Total (n=1187)
Location (Regional Health Authority #'s)				
Calgary (4)	37 %	41 %	22 %	390 (33 %)
Edmonton(10)	36 %	46 %	18 %	338 (28 %)
Southern Alberta (1-3,5)	24 %	46%	30 %	152 (13 %)
Central Alberta (6-9)	39 %	44 %	17 %	160 (14 %)
Northern Alberta (11-17)	31 %	46 %	13 %	147 (12 %)
Location: Rural-Urban				
Urban	84 %	76 %	77 %	79 %
Rural	16 %	24 %	23 %	21 %

Table 4.3 Cross Tabs of Age Group by Surgery and Type of Surgery (Breast Conserving vs Mastectomy) for the Group with Appointment $\leq$ 90 Days from Diagnosis (n=1187).

Age	< 50 (n=409, 34%)	50 - 69 (n=527, 44%)	$\geq$ 70 (n=251, 22%)	Total (n=1187)
Surgery				
Yes	96 %	95 %	90 %	94 %
No	4 %	5 %	10 %	6 %
Type of Surgery				
Mastectomy	43 %	41 %	45 %	42 %
Breast Conserving	57 %	59 %	55 %	58 %
Radiation following Breast Conserving Surgery				
	(n=225)	(n=295)	(n=125)	(n=645)
Yes	92%	86 %	60 %	83 %
No	8 %	14 %	40 %	17 %
Standard Local Treatment: Either Mastectomy or Breast Conserving Surgery plus Radiation Therapy				
Yes	91 %	87 %	70 %	85 %
No	9 %	13 %	30 %	15 %

Table 4.4 Comparison of Patients Receiving Systemic Treatment with Chemotherapy, Hormone Therapy, or Either Chemotherapy or Hormone Therapy for Three Age Groups in the Group with Appointment ≤ 90 Days from Diagnosis (n=1187)

Age	< 50 (n=409, 34%)	50 - 69 (n=527, 44%)	≥ 70 (n=251, 22%)	Total (n=1187)
Chemotherapy	77 %	31 %	5 %	41 %
Hormone Therapy	27 %	53 %	63 %	46 %
Either	84 %	72 %	66 %	75 %
Neither	16 %	28 %	34 %	25 %

Table 4.5 Comparison of Cause of Death (COD) in Three Age Groups for Patients in the Group with Appointment ≤ 90 Days from Diagnosis (n=193).

Age	< 50 (n=58)	50 - 69 (n=74)	≥ 70 (n=61)	Total (n=193)
Cause of Death				
Breast Cancer	95 %	74 %	49 %	73 %
Other	5 %	26 %	51 %	27 %

4.1.2 Group with No Appointment

Tables 4.6 - 4.9 list characteristics of the no appointment group. 119 women had no appointment after diagnosis. The average age of this group was 76 years (standard deviation = 12.05), with a range of 53 years from age 46 to age 99. 4% were under 50, 22% were between 50 - 69, while 74% were age 70 or older. 11% of this group were currently married while 89% were other. Because there were so few cases in either the youngest or the middle age category, chi-square tests of significance were not applicable and this group is not subdivided by age groups within all of the tables.

9% of cases were either Stage I or II, 3% were Stage III or IV, and 88% were unknown stage. 61% were lower grades I and II, 12% were high grades III and IV, while 27% were unknown grade. Overall, 27% of this group had an unusual morphology (not ductal or lobular). Most of those who were not graded had unusual morphology: 72% of those with unusual morphology were not graded, while only 10% of those with either ductal or lobular carcinoma were not graded.

Edmonton, Calgary, and Northern Alberta were under represented in this group contributing 26%, 22%, and 11% respectively to the total of 119 persons in this group. Central and Southern Alberta were over-represented in this group comprising 19% and 22% of this group respectively which was more than their representation in the total population. 78% were urban by postal code while 22% were rural, which is very similar to the group with appointment less than 90 days from diagnosis.

78% of patients received surgery while 22% did not. Of those who had surgery, 36% had breast conserving surgery but none of these received radiation therapy. 50% of the total 119 cases received standard local treatment with mastectomy. 50% did not receive a standard local treatment as they either had no surgery or breast conserving

surgery without radiation therapy. 100% of those in the youngest age group, 69 % of those in the middle age group, and 41% of those in the oldest age group received standard local therapy.

Regarding systemic treatment, none receive chemotherapy. 29% had hormone therapy, 31% in each of the middle and oldest age groups. None in the youngest age group received any kind of systemic treatment.

34% (41) of persons in this group have died, 49% (20) from breast cancer and 51% (21) from other causes. There was no significant difference between the three age groups in cause of death. None in the youngest age group had died.

Cases with No Appointment

Table 4.6 Characteristics of No Appointment Group (n=119)

	Number (%)
Age	
Average	75.6 y (sd=12)
Range	46 - 99
Age Group	
< 50	5 (4 %)
*50-69	26 (22 %)
≥ 70	88 (74 %)
Marital Status	
Currently Married	13 (11 %)
Other	106 (89 %)
Stage	
I or II	11 (9)
III or IV	3 (3)
Unknown	105 (88)
Grade	
I or II	73 (61)
III or IV	14 (12)
Unknown	33 (27)
Morphology	
Ductal or Lobular	87 (73)
Other	32 (27)

Table 4.7 Location of Non-referred Group

Location	Number (%)
Location by Regional Health Authority	
Calgary	26 (22)
Edmonton	31 (26)
Southern Alberta	26 (22)
Central Alberta	23 (19)
Northern Alberta	13 (11)
Location by Rural / Urban	
Urban	93 (78)
Rural	26 (22)

Table 4.8 Comparison Surgery, Surgical Type, and Subsequent Hormone Therapy
Between the Three Age Groups in Non-Referred Group

Age	< 50 (n=5)	50 -69 (n=26)	≥70 (n=88)	Total
Surgery				
Yes	5 (100 %)	24 (92 %)	64 (73 %)	93 (78 %)
No	0	2 (8 %)	24 (27 %)	26 (22 %)
Type of Surgery				
Mastectomy	5 (100 %)	18 (75 %)	36 (57 %)	59 (64 %)
Breast	0	6 (25 %)	27 (43 %)	33 (36 %)
Conserving				
Standard Local Treatment: Either Mastectomy or Breast Conserving Surgery plus				
Radiation Therapy				
Yes	100 %	69 %	41 %	50 %
No	0 %	31 %	59 %	50 %
Systemic Therapy				
Chemotherapy	0	0	0	0
Hormones	0 (0)	8 (31 %)	27 (31 %)	35 (29 %)
Either	0 %	31 %	31 %	29 %

Table 4.9 Cause of Death by Three Age Groups in Non-Referred Group

Age	< 50 (n=0)	50-69 (n=2)	≥ 70 (n=39)	Total (n=41)
Cause of Death				
Breast Cancer	0	1 (50 %)	19 (49 %)	20 (49 %)
Other	0	1 (50 %)	20 (51 %)	21 (51 %)

4.1.3 Group with Appointment > 90 Days

Tables 4.10 - 4.14 gives descriptive data on the group of 83 women with an appointment more than 90 days from diagnosis. The average age of this cohort was 65 years (standard deviation=13.5), with a range of 56 years from age 34 to age 90. Thirteen (16%) were under 50, thirty-five (42%) were between the ages of 50 and 69, and thirty-five (42%) were 70 or over. 54% of this group were currently married while 46% were other. There was a non-significant shift from currently married to other from the youngest to the oldest age group.

57% were either Stage I or II, 6% were Stage III or IV, and 37% were unstaged. There was a significant difference in stage between the three age groups: 57% of patients in the oldest age group (≥ 70) were unstaged compared to 26% in the middle age group and 15% in the youngest group $p=0.011$.

68% were grades I and II, 25% were grades III and IV, while 7% were not graded. There was no significant difference in grade between the three age groups. 88% of this group had either ductal or lobular morphology. There was no significant difference between the age groups.

There were not significant differences in the age distributions from the five regions, Edmonton, Calgary, Southern, Central, and Northern Alberta, or according to postal codes divided into rural and non-rural segments. Edmonton and Central Alberta contributed a higher percentage of cases to this group than to the total cohort. They comprised 42% and 24% of this group. Calgary contributed less percentage of cases to this group than to the total cohort, with only 6%, while the Southern and Northern Alberta contributed about the same percentage of cases to this group as to the whole cohort with 15% and 13 % each.

87% received surgery while 13% did not. Of those who had surgery, 40% had breast conserving surgery and 48% of these also received radiotherapy. Only 5% of those who received more extensive surgical treatment had radiotherapy. There were differences between the three age groups regarding the types of surgery but these differences were not statistically significant.

Of those twenty-nine patients who received breast conserving surgery, 100% in the youngest age group, 50% in the middle age group and 36% of the oldest age group received radiation as well. The overall numbers were too small to attain significance. Overall 69 % of this group received standard local therapy, either mastectomy or breast conserving surgery plus radiation. 85 % of the youngest group, 74 % of the middle age group, and 57 % of the oldest age group received standard local therapy.

Only 13% of the late appointment group received chemotherapy. There was a notable difference in the percentages of each age group who received chemotherapy, 31% in the youngest group, 20% in the middle group, and none in the oldest group.

29% of this group received hormonal therapy. Proportionately more patients in the oldest age group (37%) received hormone therapy than in the youngest (15%) or the middle age group (26%) but this was not significant. 40% of these cases received either chemotherapy or hormonal therapy but there were no statistically significant differences between the age groups for receipt of systemic therapy. The percentages who received some form of systemic treatment are 46 % for the youngest age group, 40 % for the middle aged group, and 37 % for the oldest age group.

15 persons in the late appointment group have died. Eight died of breast cancer. Seven died of other causes. The difference in cause of death between the age groups was not significant.

Cases with Appointment Greater Than Ninety Days from Diagnosis

Table 4.10: Cross Tabulations of Age, Marital Status, Stage, Grade, and Morphology within Three Age Groups for the Group with a Late Appointment (n=83)

Age	< 50 (n=13)	50 - 69 (n=35)	≥ 70 (35)	Total (n=83)
Mean Age of Whole Group				65
Age Range of Whole Group				34 - 90
Age	16 %	42 %	42 %	
Category				
Marital Status				
Currently	69 %	63 %	40 %	54 %
Married				
Other	31 %	37 %	60 %	46 %
Stage				
I & II	69 %	71 %	37 %	57 %
III & IV	15 %	3 %	6 %	6 %
Unknown	15 %	26 %	57 %	37 %
Grade				
I & II	62 %	74 %	63 %	68 %
III & IV	31 %	23 %	26 %	25 %
Unknown	8 %	3 %	11 %	7 %
Morphology				
Ductal or	92 %	91 %	83 %	88 %
Lobular				
Not Ductal	8 %	9 %	17 %	12 %
or Lobular				

Table 4.11 Table of Proportion of Cases in the Late Appointment Group from Each of the Five Locations

	Calgary	Edmonton	Southern Alberta	Central Alberta	Northern Alberta
Cases (%)	5 (6 %)	35 (42 %)	12 (15 %)	20 (24 %)	11 (13 %)

Table 4.12 Cross Tabulations Of Three Category Age Group By Surgery, Type Of Surgery, and Radiation after Breast Conserving Surgery For Late Appointment Group (N=83)

Age	< 50	50 - 69	≥ 70	Total
Surgery				
Yes	85 %	91 %	83 %	87 %
No	15 %	9 %	17 %	13 %
Type of Surgery				
Mastectomy	73 %	62 %	52 %	60 %
Breast	27 %	38 %	48 %	40 %
Conserving				
Radiation after Breast Conserving Surgery				
Yes	100 %	50 %	36 %	48 %
Standard Local Treatment: Either Mastectomy or Breast Conserving Surgery plus				
Radiation Therapy				
Yes	85 %	74 %	57 %	69 %
No	15 %	26 %	43 %	31 %

Table 4.13 Comparison of Patients Receiving Systemic Treatment with Chemotherapy, Hormone Therapy, or Either Chemotherapy or Hormone Therapy for Three Age Groups In Late Appointment Group.

Age	< 50 (n=13)	50 - 69 (n=35)	≥ 70 (n=35)	Total (%)
Chemotherapy	31 %	20 %	0%	13 %
Hormone	15 %	26 %	37 %	29 %
Therapy				
Either	46 %	40 %	37 %	40 %
Neither	54 %	60 %	63 %	60 %

Table 4.14 Comparison of Cause of Death in Three Age Groups for Patients in Late Appointment Group.

	< 50 (n=1)	50 - 69 (n=4)	≥ 70 (n=10)	Total (%)
Cause of Death				
Breast	100 %	50 %	50 %	53 %
Cancer				
Other	0	50 %	50 %	47 %

4.1.4 Comparison by Cross Tabulations Between the Three Appointment Groups

Cross tabulations between appointment groups are shown in tables 4.15 - 4.25 at the end of this section. For almost all of the variables, there were significant differences between the appointment groups.

Table 4.15 shows differences in age and marital status between the three cohorts. Those with an appointment equal to or less than 90 days from diagnosis were the youngest group, while those with no appointment were the oldest group. Nearly 75% of the no appointment group were equal to or less than 70, compared to only 21% of the timely appointment group and 42% of the late appointment group. The late appointment group was about midway between the other two groups with more of the oldest age and less of the youngest group than the timely appointment group but not to the extreme of the no appointment group. The differences in age group between the three appointment groups was highly significant ($p < .001$).

Only 11% of the no appointment group were currently married compared to 66% of the timely appointment group and 54% of the late appointment group. This was highly significant ($p < .001$).

Table 4.16 shows difference in location between the three appointment cohorts. Outside of the two major centers, Southern Alberta had 80% in the timely appointment group, Central Alberta had 79%, while Northern Alberta had 86%. Southern and Central Alberta both had a comparatively high percentage in the no appointment group at 14% and 11% respectively. This compares to 6% for Calgary, 8% for Edmonton, and 8% for Northern Alberta. These figures were all statistically significant ($p < .001$). All centers outside of Calgary had comparatively more cases in the late appointment group, with central Alberta having the largest number. There was no statistically significant difference between the three appointment groups in

terms of rural-urban location although those with appointments greater than or equal to 90 days had a slightly higher percentage that were more strictly rural.

Table 4.17 shows the disease and treatment variables for the three appointment cohorts. There were significant differences. 92% of the timely appointment group, compared to 73% of the no appointment group and 88% of the late appointment group had either a ductal or lobular carcinoma, the common morphology. Greater percentages in the no appointment and late appointment groups had uncommon morphology. This was statistically significant ($p < 0.001$).

The percentages of those in each of the appointment groups with a Grade I or II cancer was somewhat similar: 60% in the timely appointment group, 61% in the no appointment group, and 68 % in the late appointment group. The biggest differences were between the percentages who had unknown grade: 11% in the timely appointment group, 27 % in the no appointment group, and 7 % in the late appointment group. These differences were statistically significant ($p < 0.001$).

The differences between the three appointment groups in stage were statistically significant. 76% in the timely appointment group, 9% in the no appointment group, and 56% in the late appointment group had either Stage I or II cancer, whereas 13% in the timely appointment group, 88% in the no appointment group, and 37% in the late appointment group had an unknown stage. The fact that so few in the no appointment group have a stage recorded in the registry is directly related to the fact that these cases were not referred for an appointment and any stage data was often not available. Statistical significance was $p < .001$.

Table 4.18 illustrates differences in the proportion of cases receiving standard local treatment between the three appointment groups. Standard local treatment was counted as either mastectomy or breast conserving surgery plus radiation. 85% of those in the timely appointment group had some form of local treatment that was

considered standard. This compares to 50 % in the no appointment group and 69 % in the late appointment group. More in the timely appointment group (58%) had breast conserving surgery rather than a mastectomy. This compared to 36% in the no appointment group, and 40% in the late appointment group ($p < 0.001$).

83 % of those in the timely appointment group received radiotherapy after breast conserving surgery. 0 % in the no appointment group and only 48 % in the late appointment group received radiotherapy after breast conserving surgery. This was also statistically significant ($p < 0.001$).

Table 4.19 illustrates differences in systemic treatment of cases in the three appointment groups. 41% of cases in the timely appointment group and 13% of those in the late appointment group received chemotherapy. 46% of cases in the timely appointment group and 29 % in both the no appointment and the late appointment groups received hormone therapy. 75 % in the timely appointment group, 29 % in the no appointment group, and 40% in the late appointment group received some form of systemic therapy, either hormone therapy and/or chemotherapy. The differences in percentage of cases receiving some type of systemic treatment were statistically significant.

Table 4.20 illustrates the differences between the three groups in terms of receiving any treatment for which a referral would be necessary. In the appointment group, 70% of cases received such treatment, while 0% in the no appointment group, and only 27% in the late appointment group received such treatment.

Table 4.21 shows differences in vital status between the appointment groups. 84% in the timely appointment group, 66% in the no appointment group, and 82% in the late appointment group are still living, making a significant difference in mortality between the three groups ($p < 0.001$). Of those who have died, 73% in the timely

appointment group, 49% in the no appointment group, and 53% in the late appointment group have died from breast cancer instead of any other cause.

In summary, the three appointment groups appear to be different population types. They are different demographically and by disease variables. The no appointment group stands out as being composed of older, not currently married cases who are more likely not to live in a major urban center, and especially not in Calgary. They were more likely to have an unusual morphology, unknown stage, and unknown grade. A greater percentage had no surgery, while those that did have surgery were less likely to have a breast conserving operation and none of these had radiation therapy. In addition, the no appointment group was less likely to get any kind of systemic therapy. A greater percentage of these cases have died and they were much more likely to die of a cause other than breast cancer. This is quite logical, as many were older and would be expected to have associated comorbidity, which would increase the likelihood that they would succumb to some disease other than breast cancer.

The late appointment group, nearly 60% of whom were seen between 3-6 months after their diagnosis, represents to me those who are late, but who basically had an appointment and so belong as part of the appointment group. The intention was to have an appointment. Perhaps the prognosis of these individual cases looked good so that referral didn't need to be hastened, or perhaps there were other reasons, both patient and institutional, why these patients were late. The fact that only 27% of them actually received treatments that necessitated a referral seems to verify this position.

Table 4.22 illustrates the differences between regions in the incidence of what would be considered standard local treatment, either mastectomy or breast conserving surgery plus radiation therapy. All locations except Southern Alberta had over 80 % of patients receiving what would be considered standard local treatment. Southern Alberta had only 64 % receiving standard local treatment. There was no

less breast conserving surgery in any of these locations than in Edmonton. 51% of patients in Edmonton had breast conserving surgery, compared to 54% in Southern Alberta, 49% in Central Alberta, and 55% in Northern Alberta. Calgary had the highest level of breast conserving surgery at 64%. Edmonton had the highest level of accompanying radiation following breast conserving surgery at 90%. Calgary had an accompanying rate of radiation at 80%. Southern Alberta had accompanying radiation therapy much less often at 47%. However, the rates for Central and Northern Alberta were comparable to that of the major centers at 83%.

Table 4.23 illustrates the differences in treatment with any systemic therapy between the five locations. Southern Alberta, which was significantly associated with having no appointment, was among the highest in terms of systemic treatment, either chemotherapy or hormone therapy, for patients. 75 % of Calgary cases had systemic treatment, followed by 73% in Southern Alberta and 70% in Central Alberta. Edmonton and Northern Alberta had the least numbers of patients who received systemic therapy at 64% and 60% respectively.

Table 4.15. Cross Tabulations of Age Group and Marital Status by Appointment Group

		Timely Appointment N=1187	No Appointment N=119	Late Appointment N=83
Age, Mean		57 years	76	65
Age Range		15 - 95	46 - 99	34 - 90
Age Group	<50	35 %	4%	16 %
	50 - 69	44 %	22 %	42 %
	≥70	21 %	74 %	42 %
Marital Status	Currently Married	66 %	11 %	54 %
	Other	34 %	89 %	46%

Table 4.16 Cross Tabulation of Location by Appointment Group

		Timely Appointment N=1187	No Appointment N=119	Late Appointment N=83
Location	Calgary	93 %	6 %	1 %
	Edmonton	84 %	8 %	8 %
	Southern Alberta	80 %	14 %	6%
	Central Alberta	79 %	11 %	10 %
	Northern Alberta	86 %	8 %	6 %
Rural/Urban	Urban	79 %	78 %	72 %
	Rural	21 %	22 %	28 %

Table.4.17 Cross Tabulation of Disease Variables by Group

		Timely Appointment N=1187	No Appointment N=119	Late Appointment N=83
Morphology	Ductal /	92 %	73 %	88 %
	Lobular			
	Other	8 %	27 %	12 %
Grade	I or II	60 %	61 %	68 %
	III or IV	29 %	12 %	25 %
	Unknown	11 %	27 %	7 %
Stage	I or II	76 %	9 %	57 %
	III or IV	11 %	3 %	6 %
	Unknown	13 %	88 %	37 %

Table 4.18 Cross Tabulations of Standard Local Treatment, (either Mastectomy or Breast Conserving Surgery plus Radiation), by Appointment Group

		Timely Appointment N=1187	No Appointment N=119	Late Appointment N=83
Local Treatment	Standard	85 %	50 %	69 %
	Not Standard	15 %	50 %	26 %

Table 4.19 Cross Tabulation of Systemic Treatment, (either Chemotherapy or Hormone Therapy), by Group

		Timely Appointment N=1187	No Appointment N=119	Late Appointment N=83
Systemic Treatment	Yes	75 %	29 %	40 %
	No	25 %	71 %	60 %

Table 4.20 Cross Tabulation of Treatment by either Radiation and/or Chemotherapy by Group.

		Timely Appointment N=1187	No Appointment N=119	Late Appointment N=83	Total N=1389
Treatment with Chemotherapy &/or Radiation	Yes	70 %	0 %	29 %	62 %
	No	30 %	100 %	71 %	38 %

Table 4.21 Cross tabulation of Vital Status and Cause of Death by Group

		Timely Appointment N=1187	No Appointment N=119	Late Appointment N=83
Vital Status	Alive	84 %	66 %	82 %
	Dead	16 %	34 %	18 %
Cause of Death	Breast Cancer	73 %	49 %	53 %
	Other	27 %	51 %	47 %

Table 4.22 Cross-tabulations of Standard Local Treatment by Location for All Three Appointment Groups. N=1283, Missing=106, Total=1389

Standard Local Treatment		Yes	No
Location	Calgary	81 %	19 %
	Edmonton	86 %	14 %
	Southern Alberta	64 %	36 %
	Central Alberta	83 %	17 %
	Northern Alberta	84 %	16 %

Table 4.23 Cross Tabulations of Systemic Treatment with either Chemotherapy or Hormone Therapy by Location across All Three Appointment Groups. N=1389.

Chemotherapy or Hormone Therapy		Yes	No
Location	Calgary	75 %	25 %
	Edmonton	64 %	36 %
	Southern Alberta	73 %	27 %
	Central Alberta	70 %	30 %
	Northern Alberta	61 %	39 %

4.2 Results of Univariate Logistic Regression

All of the variables discussed above were entered into a univariate logistic regression in which the outcome was whether or not patients were in the timely appointment group. Only the timely appointment and no appointment groups are shown in this univariate analysis ($n: 1187+119=1306$). Differences in significance with the addition of the late appointment patients ($n=83$) to either the appointment and no appointment group will be presented for discussion.

Table 4.24 shows the odds ratios, confidence intervals, and p-values for univariate logistic regressions for the demographic and disease variables that may have significance to appointment group status.

Age, stage, grade, marital status, and location were all significant predictors of being non-referred. Age over seventy was associated with a ten-fold increase in the likelihood of not having an appointment when compared with all under 70 ($p<0.001$), and nearly thirty-fold increase in the likelihood of not having an appointment when compared with only those under 50 ($p<0.001$). Age fifty to sixty-nine was associated with a four fold increase in the likelihood of not having an appointment ($p=0.005$) compared to those under fifty.

The not currently married category had a fifteen times increased likelihood ($p<0.001$) of not having an appointment. Having a high stage tumour was not associated with any increased likelihood of not having an appointment over those who had low stage tumours. However, having an unknown stage tumour increased the likelihood of not having an appointment over fifty times ($p<0.001$).

Patients with high grade tumours were significantly more likely to have an appointment ($p=0.002$), while those with unknown grade tumours were significantly more likely to not have an appointment ($p=0.001$).

Morphology other than ductal or lobular carcinoma, called unusual morphology, had a significant odds of not having an appointment ($p < 0.001$).

Table 4.25 shows odds ratios, confidence intervals and p-values for location.

Location. There was a significant odds that those persons resident in Southern or Central Alberta would not having an appointment ($p=0.001$ and 0.011). Rural location was not significant.

Therefore, based on univariate analyses, the variables that should be included in a multivariate regression were age as a dichotomous or trichotomous variable, marital status, stage as a trichotomous variable, grade as a trichotomous variable, and location as a five category variable.

Table 4.24: Univariate Logistic Regression Analysis of Effect of Variables.

Likelihood of being in No Appointment Group (n=119) versus the Appointment group (n=1187).

		Odds Ratio	Confidence Interval	p- value
Age at	Continuous	1.11	1.09 - 1.13	< 0.001
Diagnosis				
Age (2 classes)	<70	1		Reference
	≥70	10.59	6.87 - 16.31	< 0.001
Age (3 classes)	<50	1		Reference
	50 - 69	4.04	1.54 - 10.60	0.005
	≥70	28.68	11.49 - 71.58	< 0.001
Marital Status	Currently Married	1		Reference
	Other	15.74	8.74 - 28.36	< 0.001
Stage	I or II	1		Reference
	III or IV	1.82	0.50 - 6.62	0.362
	Unknown	57.40	30.12 - 109.37	< 0.001
Grade	I or II	1		Reference
	III or IV	0.40	0.22 - 0.72	0.002
	Unknown	2.35	1.49 - 3.71	< 0.001
Morphology	Ductal or Lobular	1		Reference
	Other	4.33	2.74 - 6.84	< 0.001

Table 4.25: Univariate Logistic Regression Analysis for Location. Likelihood of being in No Appointment Group (n=119) versus the Appointment group (n=1187).

		Odds Ratio	Confidence Interval	p- value
Location	Calgary	1		Reference
	Edmonton	1.38	0.80 - 2.36	0.248
	Southern Alberta	2.57	1.44 - 4.56	0.001
	Central Alberta	2.16	1.20 - 3.89	0.011
	Northern Alberta	1.33	0.66 - 2.65	0.424
Urban or Rural	Urban	1		Reference
	Rural	1.04	0.66 - 1.64	0.874

4.3 Testing Model Robustness by Addition of Late Appointment Group

Adding the 83 patients with late appointments to the timely appointment group resulted in a slightly diminished but still significant effect of age seventy and over and age fifty to sixty-nine compared to under fifty. The effect of age was diminished because adding the late appointment group to the timely appointment group increased the mean age of that appointment group slightly towards the mean age of the no appointment group. The effect of marital status remained the same. The effect of unknown stage, unknown grade, and high grade was very similar. There was no difference in the effect that unknown morphology had. Location in either Southern or Central Alberta remained significant. Rural location was not significant.

Adding the 83 patients with late appointments to the no appointment group again resulted in a significant but slightly diminished effect of both age groups, seventy and over, and fifty to sixty-nine, on referral status. The effect was diminished because adding the late appointment group to the group without an appointment lowered the mean age of the no appointment group. The effect of not being currently married was significant but markedly decreased (odds ratio 4.79, 95% confidence intervals 3.45-6.65, $p < 0.001$) as the late appointment group added to the no appointment group increased the total percentage of currently married patients. The effect of unknown stage and unknown grade was not as great with this mix of patients but still significant. The effect of unusual morphology, although still significant was somewhat decreased. Rural location was again not significant.

The biggest difference that adding this group to the no appointment group was that location in Edmonton (odds ratio 2.46, 95% confidence intervals 1.57 - 3.86, $p < .001$) and Northern Alberta (odds ratio 2.05, 95% confidence intervals 1.17 - 3.62, $p = 0.013$) are both significant for no appointment, while being in Central Alberta (odds ratio 3.38, 95% confidence intervals 2.06-5.56, $p < .001$) or Southern Alberta (odds ratio 3.15, 95% confidence intervals 1.89-5.24, $p < .001$) carries an even greater risk of no appointment.

Chapter 5 - Multiple Logistic Regression Analysis

5.0 *Introduction*

This chapter describes the results of multivariate logistic regression to determine which variables were significant to appointment group status. An automatic, forward stepwise model and an investigator controlled, forward stepwise model will be described and compared. The stepwise models will then be compared to the final model. The final model described is an investigator controlled model.

Logistic regression was the multivariate analysis chosen to test whether some groups of patients were less likely to have a timely appointment based on demographic characteristics. The benefits of this method were previously outlined in chapter 3. Logistic regression gives an odds ratio of the likelihood that patients will not have an appointment at a specialized cancer treatment center, the question in point. The confidence intervals around the odds ratio are a measure of significance.

5.1 *Selection of Variables for the Logistic Regression Model*

Logistic regression requires data from each case for every variable. Cases with any missing data are dropped from the analysis. Therefore, all variables were checked for completeness of data so that no subjects were lost from the study. Unknowns were given a value, for instance, unknown stage and unknown grade.

Tables 4.24 and 4.25 show the p-values of univariate logistic regression for demographic, disease, and location variables. Variables with significance at $p < 0.2$ level in a univariate regression were considered for entry into the multivariate model. These included age, marital status, stage, grade, morphology, and location. The main

effects being tested were age group at diagnosis (under 50, 50-69, and 70 or over), marital status (currently married or other), and location of residence (Calgary, Edmonton, Southern Alberta, Central Alberta, and Northern Alberta). Control variables were cancer stage (low, high, unknown), tumor grade (low, high, unknown), and morphological type (2 categories: ductal and/or lobular vs other). In addition to the main effect and control variables, if a significant interaction was found between any of these variables, then an interaction variable would have to be included in the model.

Table 5.1 shows a cross tabulation of stage and appointment group. Stage was found to be highly correlated with the outcome variable, appointment group. 88% of the no appointment group were unstaged, while only 13% of the appointment group were unstaged. Because so few patients in the no appointment group were staged, stage ceased to be a valid control variable for analyzing appointment group status. If stage is not a valid control variable it can be legitimately left out of the logistic regression equation. It was elected to leave stage out of the final model and use International Classification of diseases for Oncology grade, and International Classification of diseases for Oncology morphology as control variables instead. 73% in the no appointment group and 89% in the appointment group were graded. All patients in each of the groups had a morphology. An alternate method of handling this situation would be to simply remove all unstaged patients from the study. Removing all unstaged patients from the analysis, leaves only fourteen patients in the no appointment group. No conclusions could be drawn from a study with nearly 90% of one outcome group excluded, so this was not an option.

Having an unknown stage could also be viewed as an outcome in itself, a proxy for having no appointment. If this hypothesis were true, than the variables that predict having no appointment would also predict unknown stage. This hypotheses was tested using unknown stage (formulated as a dichotomous variable, known or unknown stage) as an alternate outcome in the final logistic regression model. These

results will be discussed after the results for appointment group, because it is important to understand the depth of correlation between unknown stage and the no appointment group.

5.2 Investigator Controlled Stepwise Logistic Regression Model

An investigator controlled forward stepwise logistic regression model was constructed. Variables were added one at a time according to their significance, indicated by the likelihood ratio statistic (difference in the - 2 log likelihood between a model with a variable and the same model without that variable). This method focuses on the statistical order of importance of the variables. The order that they are listed shows their relative statistical strength. Using this approach also highlights the effects of one variable that may be hidden within another. For instance, in this regression, it can be seen that age is a confounder of marital status. When marital status is added to the regression model, the effect of age is considerably lessened. This process serves to validate the model in which the investigator puts in all of the appropriate variables at once. The variables, in order of statistical importance, are age, marital status, morphology, grade, and location. They will be discussed in turn.

Tables 5.2 - 5.6 illustrate the steps in the investigator controlled stepwise regression. The first variable entered was age (under 50, 50 to 69, 70 and over) because it had the highest likelihood ratio among all of the variables in the univariate logistic regression. The odds ratio for cases that are age 70 plus being in the no appointment group was 28.70 (95% confidence intervals 11.49 - 71.58, $p < 0.001$), while the odds ratio for cases 50-69 was 4.04 (95% confidence intervals 1.54 - 10.60, $p < 0.001$).

Marital status was the second variable entered. The odds ratio was 9.08 (95% confidence intervals 4.96 - 16.64, $p < 0.001$) that a not currently married woman would be in the no appointment group. The two older age groups were still significantly more likely to be in the no appointment group, but the odds ratio for the

oldest age group (70 and over) was about one half what it had been in the first step. Therefore, some of the effect of marital status was mediated through age group when the marital status variable was not in the model.

The dichotomous variable for morphology had the next greatest likelihood ratio in the univariate regression. Therefore, it was the next variable added. The odds ratio was 3.10 (95% confidence intervals 1.81 - 5.30, $p < 0.001$) that cases with unusual morphology would be in the no appointment group, controlling for variables already entered. The addition of the morphology variable modified the estimates for the age and marital status variables slightly. The odds ratio for cases 70 and over came down to 12.9 from 14.3, while the odds ratio for cases that were not currently married came down very slightly to 8.95 from 9.01.

Grade was the next variable entered. Unknown grade was not significant but high grade (III & IV) was. Cases with high grade were less likely to be in the no appointment group. The odds ratio was 0.48 (95% confidence intervals 0.26 - 0.90, $p = 0.022$). The addition of grade had little effect on the odds ratios for age or marital status, but the odds ratio for unusual morphology was reduced from 3.10 to 2.58, indicating that some of the effect of the morphology variable was reflected in grade.

Location in either Southern Alberta or Central Alberta was statistically significant for being in the no appointment group, controlling for the other variables. The odds ratios for southern Alberta were 2.51 (95% confidence intervals 1.29 - 4.88, $p = 0.007$) For Central Alberta the odds ratios were 2.48 (95% confidence intervals 1.24 - 4.98, $p = 0.011$). Adding this variable slightly reduced the influence of age 70 and over. The final step of this model is exactly the same as the model in which the investigator entered all of the variables at once. These results will be discussed after a review of the automatic forward stepwise model.

5.3 Automatic Forward Stepwise Logistic Regression Model

Table 5.7 illustrates the final step in the automatic forward stepwise logistic regression. In the automatic forward stepwise regression, the same significant variables from the univariate regressions were entered including age, marital status, morphology, grade, and location.

The outcome, illustrated in table 5.7, is exactly the same as the outcome from the investigator controlled forward stepwise logistic regression. However, the order of entry differed slightly. In the automatic process, location was entered prior to grade. One advantage of the automatic process is that the chi-square and p-values of each variable, both in and outside the model, is changed at every step. The investigator enters variables based on univariate p-values. In the automatic process, it was evident that the statistical significance of grade was decreased once the morphology variable was entered. Therefore, in the automatic stepwise regression, the location variable was entered prior to the morphology variable. The final step, however, is exactly the same in the two models as is evident from the table.

Both the investigator controlled and the automatic forward stepwise regression models served to verify the final model chosen by the investigator.

5.4 The Investigator Controlled Logistic Regression Model

In the investigator controlled, logistic regression model, all of the independent effect variables and the control variables were significant. The effect variables were age group, marital status, and location, while the control variables were grade and morphology.

Table 5.8 shows the results of the investigator controlled multiple logistic regression.

Age group 50 - 69 had an odds ratio of 2.8 (95% confidence intervals 1.03 - 7.46, $p=0.043$) of not having an appointment. Age group 70 and over had an odds ratio of 11.6 (95% confidence intervals 4.49 - 29.75, $p\leq 0.001$) of having no appointment.

Not being currently married had an odds ratio of 8.98 (95% confidence intervals 4.85 - 16.62, $p < 0.001$) of having no appointment.

Low grade (I and II) was used as the reference grade. Unknown grade was not significant for having no appointment. Cases with high grade (III and IV) were significantly less likely to be in the no appointment group. The odds ratio was 0.48 (95% confidence intervals .26 - .91, $p = 0.024$).

Cases that had morphologies other than ductal or lobular carcinoma had an odds ratio of 2.7 (95% confidence intervals 1.42 - 5.11, $p = 0.002$) of being in the no appointment group.

The Calgary regional health authority formed the reference location, because it had the least proportion of cases with no appointment. It is an arbitrary decision, but it seems that because the outcome is whether or not cases had an appointment, the location with the least proportion of cases in the no appointment group should be the reference value. This is similar to choosing age less than 50 as the reference age group as there were the least proportion of cases with no appointment in this age group. The other age groups can then be compared to the reference.

There was a significant odds ratio of not having an appointment (compared to the Calgary reference) for those living in the Southern Alberta, odds ratio 2.5 (95% confidence intervals 1.29 - 4.88, $p=0.007$), and for those in Central Alberta, odds ratio 2.5 (95% confidence intervals 1.24 - 4.98, $p=0.011$). There was no statistically significant difference between Calgary and either Edmonton or Northern Alberta.

5.4.1 Interaction Variables

Interaction variables were constructed to assess whether the effect of any one variable was different for the different categories of any other variable. For instance, does marital status have a different effect in age 70 and over than in either of the younger categories? In order to determine this, interaction variables are tested in a multiple logistic regression model for significance. If any are found to be significant, it means that the effect of a variable is different for different categories of another variable. This is called effect modification.

Interaction variables were constructed from combining each of the variables in the investigator controlled model as product terms, resulting in ten extra variables: location*age, location*marital status, location*grade, location*morphology, age*grade, age*marital status, age*morphology, marital status*grade, morphology*grade, and morphology*marital status. They were added to the investigator controlled model one at a time. Of particular interest would be interaction between location and either age or marital status or age and marital status (the example cited). None of these variables were significant and, therefore, none of the interaction variables were included in the model. In other words, there were no significant effect modifiers.

5.4.2 Goodness of Fit of the Logistic Regression Model

Table 5.9 shows the goodness of fit test categories. The measure of fit used in this analysis was the Hosmer and Lemeshow C statistic. As was discussed in the materials and methods, Section 3.5.3, this is a Pearson chi-square measure of the conformity of observed to expected values when the data are ordered into deciles⁹⁸. The expected values for group=1 are those for the outcome of being in the no appointment group. The expected values for group=0 are those for the likelihood of

being in the appointment group. The C statistic of the Hosmer and Lemeshow test for the final model was 3.5906, $df=8$, $p = 0.8920$. The high p-value indicates a very close correlation between the observed data and what would be expected according to the hypotheses. Therefore, this model has a good fit.

5.4.3 *The Final Model*

Table 5.8 shows odds ratios, confidence intervals and p-values of the final logistic regression model. The final model contains no interaction factors so, in essence, it is the investigator controlled model which is exactly the same as the stepwise models, both automatic and investigator controlled. This model, testing for no appointment, contained five variables, two effect variables, two control variables, and one variable that was both effect and control. Trichotomous age was both an effect and a control variable. Marital status and location were both effect variables, while grade and morphology were the control variables. After working through all of the models, the final model gives an answer to the question, do demographic patterns influence referral to a cancer specialist. The answer is in the affirmative. Cases with location in Southern and Central Alberta or cases who are not currently married, all have significantly increased odds of having no specialist appointment, controlling for age, grade, and morphology. Older age is also a significant predictor of having no appointment.

5.5 Measure of Robustness of the Model

Eighty-three patients had an appointment over ninety days from diagnosis. They weren't considered in the referred group, who by definition had an appointment within ninety days from diagnosis. Nor were they considered part of the non-referred group because these cases did have an appointment even if it was late. In a test of robustness of the model, it was decided to treat these cases first as part of the referred group and then as part of the non-referred group. The model is considered robust if it fits a wider population than the population sample in question.

Table 5.10 shows the effects of adding the eighty-three late cases to the group with an appointment. The effect of age was lessened. There was no significant difference in referral between those 50-69 and those <50. This would be expected as the average age of this group was older than of the original referred group. Therefore, age would not figure so much in referral if these cases were part of the referred group. The effect of marital status, grade, and morphology were nearly the same as in the original group. The effect of location was lessened very slightly.

There was no evidence of interaction between any of the final model variables when tested with this expanded group. Including the extra cases in the referred group resulted in the Hosmer and Lemeshow Goodness-of-Fit Chi-square was 4.0458, df=8, $p = 0.8530$, indicating a good fit of the model with the extra cases added to the appointment group.

Table 5.11 shows the effects of treating the 83 late appointment cases as part of the no appointment group. The addition of these cases decreased the average age of the no appointment group. This decreased the effect of age on appointment group status but age was still significant. Age ≥ 70 had an odds ratio 6.55 (95% confidence interval 3.8 - 11.3, $p < 0.001$) and age between 50 -69 had an odds ratio of 2.13 (95% confidence interval 1.2-3.7, $p = 0.008$) of being in the no appointment group. The

effect of being not currently married was decreased but still significant with an odds ratio of 3.06 (95% confidence interval 2.14-4.38, $p < 0.001$) for being in the no appointments group. The effect of high grade became non-significant with odds ratio of 0.66 (95% confidence interval 0.43-1.01, $p = 0.060$) but the effect of unusual morphology remained with odds ratio of 2.31 (95% confidence interval 1.38-3.87, $p = 0.001$). The biggest difference made by adding the 83 late referrals to the no appointment group was in the significance of location. Every location outside of Calgary had a significantly higher incidence of having no appointment. Edmonton had an odds ratio of 3.04 (95% confidence interval 1.85-5.00, $p < 0.001$), southern Alberta had an odds ratio of 2.96 (95% confidence interval 1.70-5.15, $p = 0.001$), central Alberta had an odds ratio of 4.14 (95% confidence interval 2.39-7.18, $p < 0.001$), while northern Alberta had an odds ratio of 2.20 (95% confidence interval 1.17-4.09, $p = 0.013$).

No interaction variables were significant although the location*marital status variable tended towards significance. The interaction variables were not kept in the model. The Hosmer and Lemeshow goodness of fit statistic was 6.95, $df = 8$ $p = 0.5423$. This indicated a good model fit with the addition of the 83 late cases to the no appointment group.

The addition of the late appointment group to either the timely appointment group or the no appointment group results in a model similar to the final model. The importance of location is emphasized when the late appointment cohort is part of the no appointment group. These additions provide evidence of a robust final model.

5.6 Conclusion

The primary objective of this thesis was to determine bias in referral of breast cancer patients to specialized consultation and treatment services in Alberta, by a systematic exclusion of some groups of patients based on socio-demographic, clinical, and/or tumour factors. This study provides evidence that the socio-demographic variables, age, marital status, and location do contribute to decisions about whether to refer breast cancer patients for further consultation or treatment.

The effect of age on appointment status was significant and appeared to be province wide. This effect was not unexpected considering that treatment with radiation or chemotherapy at Alberta Cancer Board facilities was not always considered necessary according to the clinical practice guidelines available in 1997. Women between 50-69 are often recommended tamoxifen, especially if they are estrogen receptor positive, instead of chemotherapy. Therefore, they might not need a referral either.

For women age 70 and over, tamoxifen was recommended by the clinical practice guidelines, even for those women who were estrogen receptor negative. Although radiation therapy is standard treatment with breast conserving surgery, neither chemotherapy nor radiation therapy have been tested in women age 70 and over, so the use of these forms of treatment may not be routine in this age group. Because tamoxifen therapy does not require a referral to the Alberta Cancer Board, these patients might not have an appointment. The database does have a field for hormonal treatment (usually tamoxifen) but this information may have been missing for patients who did not have an appointment. The database does not contain information about hormone receptor status, a variable important to both treatment and prognosis.

There is a possibility that some physicians would have contacted an oncologist at an Alberta Cancer Board center, outlined the case and gotten a recommendation to start tamoxifen. These types of informal consultations would not be recorded in the

appointments database, therefore this study would have missed this kind of consultation. Appointments are made and documented in the Alberta eXtensible Oncology Network (AXON) database by the admissions department, not by physicians.

A second reason why older cases may be less likely to have an appointment is that they are more likely to have co-existing illnesses that could alter their treatment possibilities. Information on co-morbidity was unavailable on the cancer registry database, so that this important prognostic variable could not be controlled for. Controlling for co-morbidity may have decreased the influence of age on appointment group status although, considering the literature, this likely would not account for all of the variation.

The effect of marital status on appointment status was surprising. Many of these women had been married but were widowed as they grew older. However, even adjusting for age as a continuous variable (which was done but is not shown), marital status was still significant for having no appointment. Marital status represents a level of social support the importance of which is difficult to gauge. Factors like mental, physical, and emotional health are affected. Marital status may also be involved in transportation problems or just the logistics of having therapy that may be time consuming and sometimes debilitating. There may also be differences in the dynamics of physician patient communication for those who are not currently married. None of these factors were available on the database, but all of them could have been influential for appointment group. This study was not designed to address these factors but the fact that marital status was highly significant suggests that these may be important.

Location in Central and Southern Alberta, outside of the two major urban centers, was significant for having no appointment. It was surprising that it wasn't the more sparsely populated and geographically distant North that had the higher proportion of

cases with no appointment. It would be interesting to know if there are organizational structures in place in Northern Alberta that ensure that cancer patients get Alberta Cancer Board specialist appointments. The differences in treatment patterns between regions in Alberta could reflect variations between physicians, hospitals, and different regions. These factors were not available on the database and so could not be controlled. Where the variation lies, is not known. Interestingly, purely rural status, that is, not living in a city town or village was not significant to appointment group status.

The stage of cancer was not available for a sizeable percentage of cases. For cases with an appointment but unknown stage, it is almost certain that the stage was known but either not recorded or recorded in an unusual location in a large chart that was missed by the coders. For cases with no appointment, again it is most likely that stage was known by the patient's treating physician. This information may not always accompany the pathology or cytology reports that are sent to notify the Alberta cancer registry in fulfillment of provincial legislation and therefore, the registry does not have this information.

Stage is a very important variable and for most studies of treatment or survival, cases with an unknown stage would be dropped. This analysis was not of treatment or survival, but of appointment group status and to some extent, the unknown stage was like a proxy for having no appointment. 88% of those in the no appointment group also had an unknown stage. The presumption that unknown stage was like a proxy for no appointment was tested in a logistic regression analysis using known and unknown stage as the dichotomous outcome variable. The variables tested were the same as those in the logistic regression analysis of appointment group status.

Table 5.12 shows the results of the logistic regression using unknown stage as the outcome. Age 70 and over, and a not currently married status were significant although the odds ratios and confidence intervals were considerably less than testing

for no appointment. Unusual morphology and unknown grade were also significantly more likely to have an unknown stage while high grade was significantly less likely to have an unknown stage. Location in Edmonton as well as in Southern and Central Alberta was significant for unknown stage.

These results verify the assumption that unknown stage is, to some extent, a proxy for the no appointment group. As stage will be used in the survival analysis, this comparison could be quite useful. Therefore, although knowing that stage is crucial for treatment and survival considerations, in this study, unknown stage will be of value in the analysis.

Table 5.1 Cross Tabulation of Appointment Group by Stage

	Timely Appointment	No Appointment
Stage I and II	902 (76%)	11 (9%)
Stage III and IV	135 (11%)	3 (3 %)
Stage Unknown	150 (13%)	105 (88%)

Table 5.2 First Step of Investigator Controlled Stepwise Logistic Regression. Age (<50, 50-69, ≥70) entered.

Variable		Odds Ratio	Confidence Intervals	p-value
Age	<50	1		reference
	50-69	4.04	1.54 - 10.60	0.005
	≥70	28.68	11.49 - 71.58	<0.001

Table 5.3 Second Step of Investigator Controlled Stepwise Logistic Regression.
Marital Status entered.

Variable		Odds Ratio	Confidence Intervals	p-value
Age	<50			
	50-69	3.09	1.16 - 8.23	0.024
	≥70	14.28	5.62 - 36.25	<0.001
Marital Status	Currently Married			
	Other	9.08	4.96 - 16.64	<0.001

Table 5.4 Third Step of Investigator Controlled Stepwise Logistic Regression.
Morphology entered.

Variable		Odds Ratio	Confidence Intervals	p-value
Age	<50	1		reference
	50-69	2.95	1.11 - 7.88	0.031
	≥70	12.94	5.07 - 32.99	<0.001
Marital Status	Currently Married	1		reference
	Other	8.95	4.87 - 16.47	<0.001
Morphology	Ductal or Lobular	1		reference
	Other	3.10	1.81 - 5.30	<0.001

Table 5.5 Fourth Step of Investigator Controlled Stepwise Logistic Regression.
Grade Entered.

Variable		Odds Ratio	Confidence Intervals	p-value
Age	<50	1		reference
	50-69	2.86	1.07 - 7.65	0.036
	≥70	12.07	4.72 - 30.83	<0.001
Marital Status	Currently Married	1		reference
	Other	8.97	4.87 - 16.52	<0.001
Morphology	Ductal or Lobular	1		reference
	Other	2.58	1.38 - 4.84	0.003
Grade	Low	1		reference
	High (III or IV)	0.48	0.26 - 0.90	0.022
	Unknown	1.71	0.63 - 2.18	0.619

Table 5.6 Fifth and Final Step of the Investigator Controlled Stepwise Logistic Regression. Location Entered.

Variable		Odds Ratio	Confidence Intervals	p-Value
Age	<50	1		reference
	50-69	2.77	1.03 - 7.46	0.043
	≥70	11.56	4.49 - 29.75	<0.001
Marital status	Currently Married	1		reference
	Other	8.98	4.85 - 16.62	<0.001
Morphology	Ductal or Lobular	1		reference
	Other	2.70	1.42 - 5.11	0.002
Grade	Low (I & II)	1		reference
	High (III & IV)	0.48	0.26 - 0.91	0.024
	Unknown	1.27	0.67 - 2.43	0.469
Location:	Calgary	1		reference
	Edmonton	1.83	0.98 - 3.43	0.58
	Southern Alberta	2.51	1.29 - 4.88	0.007
	Central Alberta	2.48	1.24 - 4.98	0.011
	Northern Alberta	1.37	0.62 - 3.02	0.443

Table 5.7 Final Step of the Automatic Forward Stepwise Logistic Regression as Computed by SAS.

Variable		Odds Ratio	Confidence Intervals	p-value
Age	<50	1		reference
	50-69	2.77	1.03 - 7.46	0.043
	≥70	11.56	4.49 - 29.75	<0.001
Marital Status	Currently Married	1		reference
	Other	8.98	4.85 - 16.62	<0.001
Morphology	Ductal or Lobular	1		reference
	Other	2.70	1.42 - 5.11	0.002
Grade	Low (I& II)	1		reference
	High (III & IV)	0.48	0.26 - 0.91	0.024
	Unknown	1.27	0.67 - 2.43	0.469
Location:				
	Calgary	1		reference
	Edmonton	1.83	0.98 - 3.43	0.058
	Southern Alberta	2.51	1.29 - 4.88	0.007
	Central Alberta	2.48	1.24 - 4.98	0.011
	Northern Alberta	1.37	0.62 - 3.02	0.443

Table 5.8: Investigator Controlled Multivariate Model Predicting that a Patient Would be part of the No Appointment Group, (n=119), the outcome. This is the Final Model.

Variable		Odds Ratio	Confidence intervals	p-values
Age	<50	1		reference
	50-69	2.77	1.03 - 7.46	0.043
	≥ 70	11.56	4.49 - 29.75	<0.001
Marital Status	Currently Married	1		reference
	Other	8.98	4.85 - 16.62	<0.001
Grade	Low (I & II)	1		reference
	High (III & IV)	0.48	0.26 - .91	0.024
	Unknown	1.27	0.67 - 2.43	0.469
Morphology	Ductal or Lobular	1		reference
	Other	2.70	1.42 - 5.11	0.002
Location	Calgary	1		reference
	Edmonton	1.83	0.98 - 3.43	0.058
	Southern Alberta	2.51	1.29 - 4.88	0.007
	Central Alberta	2.48	1.24 - 4.98	0.011
	Northern Alberta	1.37	0.62 - 3.02	0.4431

Table 5.9 Hosmer and Lemeshow Goodness of Fit Test for the Logistic Regression Model. Group 1= Cases with No Appointment, n=119, Group 0 = Cases with Timely Appointment, n=1187.

Partition for the Hosmer and Lemeshow Test					
Partitio n	Total	Group=1		Group=0	
		Observed	Expected	Observed	Expected
1	135	0	0.32	135	134.68
2	151	0	0.65	151	150.35
3	144	0	1.07	144	142.93
4	152	1	1.89	151	150.11
5	132	3	2.77	129	129.23
6	124	6	4.66	118	119.34
7	125	9	8.55	116	116.45
8	136	22	19.20	114	116.80
9	138	43	43.06	95	94.94
10	69	35	36.84	34	32.16
Hosmer and Lemeshow Goodness-of-fit Test					
	Chi-Square	DF	Pr>ChiSq		
	3.5906	8	0.8920		

Table 5.10: Testing Model Robustness. 83 Cases with Late Appointment added to Timely Appointment Group (n=1187 + 83 = 1270), No Appointment Group (n=119)

Variable		Odds Ratio	Confidence intervals	p - Values
Age	<50	1		reference
	50-69	2.67	0.99 - 7.16	0.052
	≥ 70	10.33	4.03 - 26.49	<.001
Marital Status	Currently Married	1		reference
	Other	9.07	4.92 - 16.73	<.001
Grade	Low (I/II)	1		reference
	High (III/IV)	0.49	0.26 - 0.91	0.025
	Ungraded	1.44	0.76 - 2.72	0.261
Morphology	Ductal or Lobular	1		reference
	Other	2.46	1.32 - 4.58	0.005
Location	Calgary	1		reference
	Edmonton	1.52	0.82 - 2.83	0.185
	Southern Alberta	2.23	1.16 - 4.30	0.017
	Central Alberta	2.23	1.12 - 4.42	0.022
	Northern Alberta	1.25	0.57 - 2.75	0.581

Table 5.11: Testing Model Robustness. 83 Cases with Late Appointment added to No Appointment Group (n=119 + 83 = 202), Timely Appointment Group (n=1187)

Variable		OddsRatio	Confidence intervals	p - values
Age	<50	1		reference
	50-69	2.13	1.22 - 3.71	0.008
	≥ 70	6.55	3.78 - 11.34	<.001
Marital Status	Currently Married	1		reference
	Other	3.06	2.14 - 4.38	<.001
Grade	Low (I & II)	1		reference
	High (III & IV)	0.66	0.43 - 1.02	0.060
	Unknown	1.12	0.65 - 1.90	0.708
Morphology	Ductal or Lobular	1		reference
	Unusual	2.31	1.38 - 3.87	0.001
Location	Calgary	1		reference
	Edmonton	3.04	1.85 - 5.00	<.001
	Southern Alberta	2.96	1.70 - 5.15	<.001
	Central Alberta	4.14	2.39 - 7.19	<.001
	Northern Alberta	2.19	1.18 - 4.09	0.013

Table 5.12 Test of Stage, Known or Unknown, as a Proxy for Appointment Status

Variable		Odds Ratio	Confidence Intervals	p- Value
Age	<50	1		reference
	50-69	0.91	0.61 - 1.35	0.628
	≥70	2.64	1.75 - 3.99	<0.001
Marital status	Currently Married	1		reference
	Other	2.06	1.49 - 2.83	<0.001
Morphology	Ductal or Lobular	1		reference
	Other	2.70	1.42 - 5.11	<0.001
Grade	Low (I & II)	1		reference
	High (III & IV)	0.55	0.37 - 0.83	0.004
	Unknown	2.37	1.52 - 3.70	0.001
Location	Calgary	1		reference
	Edmonton	1.83	1.19 - 2.81	0.006
	Southern Alberta	2.98	1.82 - 4.71	<0.001
	Central Alberta	3.89	2.43 - 6.23	<0.001
	Northern-Alberta	1.50	0.85 - 2.63	0.159

Chapter 6 - Survival Analysis

6.0 *Introduction to Survival Analysis*

A survival analysis was undertaken to answer the second question of this thesis, that is, whether the length of overall survival was affected by appointment group status. If appointment group was significant, was this due to the demographic factors, age, marital status, or location, controlling for stage, grade, and morphology?

A survival analysis has as its outcome, survival time. Survival time is time until an event (failure) occurs⁹⁹. In the context of this thesis, survival time is measured from the date of diagnosis of breast cancer until the date of death from breast cancer. Cases that have not died, and cases that died from causes other than breast cancer, were censored. Censoring allows measurement of the contribution to survival of all cases that did not reach the specified event⁹⁹. Censoring measured the time from diagnosis of breast cancer until either, death from any other cause or, a predetermined cutoff time, September 30, 2001.

Survival was measured by both Kaplan-Meier survival analysis and Cox survival analysis. The Kaplan-Meier survival analysis computes a test of significance of individual variables associated with survival. The Kaplan-Meier method also provides survival curves and log minus log survival curves. The log minus log curves are a precursor to the Cox survival analysis as they are a test of the proportional hazards assumption.

Variables that satisfied the proportional hazards assumption were entered into a Cox survival analysis. The Cox survival analysis can be used as either a univariate, or a multivariate analysis, that provides a hazard ratio with confidence intervals and p-

values for a variable, controlling for all other variables in the model. Potential confounders can be controlled. Interaction factors can be tested. Tests of robustness can be done using this multivariate model.

6.1 *Kaplan-Meier Survival Analysis*

The Kaplan-Meier survival analysis computes survival curves by estimating the survival probability up to each ordered failure time, death from breast cancer, in a group. The estimated survival probability is computed using the product limit formula, the product of the probabilities of surviving past a certain time, given survival up to that time. Limiting the survival probability to product terms up to the survival time being specified leads to the name, product limit formula. Survival curves are step functions from one failure time to the next so that the curves may not appear smooth. The Kaplan-Meier survival curves can be inspected for visual evidence of difference in survival between individual variable categories.

The test of significance for the Kaplan-Meier survival analysis is the log-rank test, a chi-square analysis which uses the observed versus expected counts over categories of outcomes. The categories for the log-rank test are defined by each of the ordered failure times⁹⁹. The statistical significance of an individual variable to survival can be determined.

Table 6.1 lists the univariate significance of variables from the log-rank test in the Kaplan-Meier analysis. Variables that were statistically significant (p -value < 0.05) included appointment group, age, stage, grade, unusual morphology, any systemic treatment, and local treatment according to recommendations or not.

Marital status and the location variables were not significant at $p < 0.05$. Variables that were significant at the 0.2 level in the Kaplan-Meier were considered for entry into a

multiple Cox regression model. Therefore, the location variables were included in the multivariate Cox survival analysis but marital status was not.

Kaplan-Meier log minus log survival curves were calculated as proof of the proportional hazards assumption of the Cox survival model. These curves transform the survival data from a proportion, between 0 and 1 on the Y axis, to a distribution from minus infinity to plus infinity on the Y axis. As survival decreases, that is, goes from 1 towards 0, the value of the log minus log survival distribution function increases from a larger negative number toward zero. Therefore, the log minus log curves angle from the bottom left to the upper right. The value along the X-axis is the log of time in days. For instance, the log of 1000 days is approximately 6.9. Log minus log survival curves for two or more categories of any variable are a mathematical expression of the linear relationship that exists between the variable categories. In other words, the differences between the curves is equal to the difference in predictor values of survival or hazard between two or more categories of a variable. The assumption of proportional hazards is that the effect of any variable is constant over time. Therefore, the hazard ratio for each independent variable must remain constant over time. If the effect of the variable is constant over time, the log minus log curves will be fairly parallel. If the proportional hazards assumption is therefore satisfied, the variable can be used in the Cox survival model.

6.2 Proportional Hazards Assumption

The proportional hazards assumption for each variable was tested by visual inspection of the log - log curves. Variables that satisfy the proportional hazards assumption can be used in the Cox survival analysis. The curves for each variable are discussed below. The log minus log curves for each variable are illustrated at the end of this chapter in Figures 6.1 - 6.10.

Appointment group. The log minus log curves for the two appointment groups, either with or without an appointment, were reasonably parallel and did not cross. Therefore, the effect of appointment group status was constant over time and was considered to satisfy the proportional hazards assumption.

Age group. The log-log curves for the three age groups, (less than 50, 50-69, & 70 or over), were not parallel. The curves for under 50 and 50-69 overlapped towards the end of the curve, an indication that as time went on, survival of those 50-69 was better than that of those under 50. This was considered not satisfactory to the proportional hazards assumption and so this variable was dropped for consideration in the Cox survival analysis.

Age group. The log-log curves for the dichotomous age groups, (less than 70, 70 and over), were distinct and parallel. This did satisfy the proportional hazards assumption and this dichotomous variable was used in the subsequent Cox survival analysis instead of the three-category age variable.

Marital Status. The marital status variable did satisfy the proportional hazards assumption, although it does not satisfy the significance requirement.

Stage. The log - log curve for low stage paralleled the two curves representing high and unknown stage. The curves for high and unknown stage crossed each other three times at the beginning. The high stage breaks away from the unknown stage curve after about one third of the time and remains distinct from both unknown and low stage. Survival is worse for high stage. The effects of these categories of stage are roughly constant over time, both high and unknown stage had poorer survival than low stage. This variable was considered to satisfy the proportional hazards assumption for two reasons. First, the curves for high and unknown stage crossed each other at the beginning and secondly because the Cox survival analysis counts each of these categories as separate variables with low stage being the reference for

each of them. Both were distinct from low stage and fairly parallel to it. Therefore, their effects were constant with respect to low stage and the stage variable could be included in the Cox survival model.

Grade. The log - log curves for grade were also generally parallel. Unknown grade was totally distinct from high grade and low grade. High grade crossed over low grade very early and then continued parallel between unknown and low grade. Even though there was one distinct cross, the effects were going in the same direction in a parallel fashion and were constant over time. The cross occurred very early. This was considered to satisfy the proportional hazard's assumption.

Morphology. The log - log curves for the dichotomous morphology variable are definitely distinct and parallel. The effects of morphology status were constant over time and the proportional hazards assumption was satisfied.

Location. The log - log curves for the five-category location variable were totally indistinct, running parallel to and on top of one another. These also satisfy the proportional hazards assumption as the effects are constant over time.

Local Treatment. The log - log curves for the two category local treatment variable were parallel indicating that this variable could be entered into a Cox regression survival analysis.

Systemic Treatment. The log - log curves for the two category systemic treatment variable were not parallel and did not satisfy the proportional hazards assumption. Therefore, this variable could not be used in the Cox survival analysis.

In conclusion, all of these variables, except the trichotomous age and the systemic treatment variable, satisfied the proportional hazards assumption and could therefore be entered into the Cox survival analysis.

6.3 Cox Survival Analysis

The Cox survival analysis is a method of regression that gives an estimate of the hazard ratio for a variable. The hazard ratio gives the instantaneous potential per unit of time for an event (death from breast cancer) to occur given that the individual has survived up until that time. As the survival probability decreases, the hazard ratio increases⁹⁹. The Cox survival analysis can be modeled with one or several variables. The hazard ratio for any variable is controlled for all the other variables in the model. SAS calculates the hazard ratio with confidence intervals and p-values.

The Cox model is a 'robust' method. It does not require a baseline hazard but gives reasonably good estimates of regression coefficients and hazard ratios that usually approximate the more exact parametric model.

Variables that were significant in the Kaplan-Meier survival analysis and satisfied the proportional hazards assumption, were tested initially in univariate Cox survival analysis models. From there, variables that were significant at the $p=0.20$ were entered into investigator controlled multivariate models. Automatic forward stepwise Cox survival analyses were not used for the survival analysis because the software program did not compute class variables from categorical variables with more than two categories. Therefore, the reference category would change as one or more than one component of a categorical variable was entered into the stepwise process using the investigator computed dummy variables.

The investigator controlled multivariate model contained all remaining significant variables. The main test variable was appointment group. Secondary test variables were location, marital status, and age. Control variables, included age, stage, grade, morphology, and local treatment. These could be dropped if they were found to be not significant and if dropping them made no difference to the rest of the model.

When a model was decided with individual variables, interaction between variables was tested by adding the interaction factors one at a time to the final model and testing for significance by use of the likelihood ratio test between models with and without the interaction variables. The final model would include any significant interaction variables.

Finally the model was subjected to tests of robustness by adding the 83 cases with late appointments either to the appointment group or the no appointment group. If the model is robust, the addition of this population of patients to either appointment group should still fit the results.

6.3.1 Univariate Cox Survival Analysis

Table 6.2 lists the results from the univariate Cox survival analysis. The p-values from the univariate Cox survival analysis and the Kaplan-Meier survival analysis are almost identical. In addition, the Cox survival analysis provides a hazard ratio and confidence intervals. The statistically significant factors (at $p=0.05$) included appointment status, stage, grade, morphology, and local treatment. Age 70 and over was not significant ($p=0.055$). The not currently married status was again not statistically significant ($p=0.469$) and would not be entered into the multivariate Cox survival analysis. Some categories of the location variable were statistically

significant at levels of $p \leq 0.20$, therefore, the location variables were included in the multivariate Cox survival analysis.

6.3.2 *Investigator Controlled Cox Survival Analysis*

Table 6.3 shows the variables and associated hazard ratios, confidence intervals, and p-values from the initial investigator controlled multivariate survival analysis.

Variables that had satisfied the proportional hazards assumption and had a significance level at $p=0.20$ in the Kaplan-Meier and the univariate Cox survival analysis were entered into the multivariate Cox model. These included age 70 and over, stage, grade, morphology, local treatment, location, and appointment status. Although there is a correlation with appointment status, stage was still included in the multivariate model because it is a valid control variable in the survival analysis. There are non-staged cases in each appointment group and each age group, and there will be both staged and non-staged cases that have died. Even if the addition of non-staged group results in the test variable, appointment group, being non-significant, the thesis question about survival can still be answered.

In the multivariate Cox survival analysis, the test variable is appointment group. The control variables are stage, grade, morphology, and local treatment. A secondary test variable is location. Age is considered a test variable and a control variable.

The test variable, appointment group status, was not significant. The hazard ratio for no appointment was 1.29 (95% confidence intervals 0.72 - 2.31, $p=0.394$). The control variables, stage (high and unknown), grade (high and unknown), and local treatment were significant with hazard ratios and confidence intervals similar to those of the automatic forward stepwise survival analysis. Unusual morphology and age ≥ 70 were not significant. None of the location categories were significant.

The morphology variable was dropped from this analysis with little change seen for other variables. The age variable could also have been dropped based on its level of significance and by the fact that other variables were not changed when the age variable was removed. However, it was kept because there was some interest in whether age would interact with other variables. In like manner, location was kept. Both location and age group are test variables and it seems valuable to leave them in the model.

The individual variables left in the investigator controlled model were appointment group status (not significant but the main effect variable, so must remain), the stage and grade variables, the local treatment variable, the location variables, and age group. (Note: the SAS software program used for the Cox survival analysis enters each category of a variable as a separate variable, so that stage would be entered as high stage and unknown stage, while low stage would be the reference category, and so on for the other categorical variables: location and grade. For this reason, I refer to the stage variables, the grade variables and so on as though I were speaking of separate variables).

Tests of interaction between these variables had to be done before a final Cox survival model could be determined.

6.3.3 Interaction Factors

Interactions between all combinations of the variables left in the investigator-controlled model were estimated as product terms. They were tested one at a time in the model described above that included the appointment group, age group, stage, grade, and location variables.

There were forty-three product terms tested. Of these, three were significant: unknown grade*no appointment group; age $\geq$ 70*no appointment group; and age $\geq$ 70*unknown stage. Various combinations of these three variables resulted in different levels of significance for one or all. If all three variables were entered into the Cox model at the same time, only unknown grade*no appointment group remained significant. Two combinations between unknown grade*no appointment group and either no appointment group*age $\geq$ 70 or age $\geq$ 70*unknown stage were tried. The first combination resulted in a very wide confidence interval for the no appointment group*age $\geq$ 70 variable (hazard ratio=8.38, 95% confidence intervals 1.07 - 65.69, p-value=0.043). Therefore, it was decided to drop no appointment group*age $\geq$ 70, and use the remaining two interaction variables unknown grade*no appointment group and age $\geq$ 70*unknown stage.

The significant individual interaction variables kept were again tested in the model with their interaction counterparts. That is, the interaction variable high grade*no appointment group had to be tested with unknown grade*no appointment group in order to account for all cases. The reference variable for this would be low grade*appointment group. In like manner, the interaction variable high stage*age $\geq$ 70 had to be tested with unknown stage*age $\geq$ 70. The reference here is low stage*age $<$ 70. In this manner all of the cases are accounted for within the interaction variables. The likelihood ratio is the test of significance for these interaction variables comparing models without the interaction variables with models that have included them. In

both cases, and when all four additional interaction variables were brought into the model, the likelihood ratio test was significant.

With the addition of these interaction variables, the location variables and the no appointment group remained non-significant. Age 70 and over gained significance. Unknown grade and high grade remained significant as did high stage. Unknown stage was not significant with the addition of the interaction variables. Non-standard local treatment remained significant.

6.4 The Final Model

Table 6.4 shows the final investigator controlled Cox survival analysis model with the significant interaction factors included. For this analysis only the timely (n=1187) and the no appointment (n=119) groups were included. The group of 83 cases with no appointment was left out of this model. The final model contained five effect variables (appointment group status and four locations), six control variables (high grade, unknown grade, high stage, unknown stage, age $\geq$ seventy, and local treatment), and four interaction variables (age $\geq$ 70 * high stage, age $\geq$ 70 * unknown stage, appointment group * high grade, and appointment group * unknown grade).

In this model, no appointment, unknown stage, and location were not significant. High stage, high grade, unknown grade, and local treatment had statistically significant increased hazard ratios. Age 70 and over had a decreased hazard ratio. None of the location variables were significant. Interaction variables of age $\geq$ 70 * unknown stage and no appointment group * unknown grade were significant.

Age 70 and over had an increased hazard ratio in those with unknown stage. This is interesting considering that age 70 and over itself had a diminished hazard ratio. The

interaction variable age ≥ 70 *high stage was not significant. High stage was significant in itself, and being ≥ 70 did not add to this significance.

No appointment was significant for those with unknown grade in the interaction variable unknown grade * no appointment. The interaction variable, high grade*no appointment was not significant as high grade alone is hazardous and having no appointment does not add to that hazard.

In the final model, high stage, high and unknown grade, age 70 and over in those with unknown stage, and no appointment in those with unknown grade are all significant to survival.

This answers one question of the thesis, is appointment group important to survival? The answer is yes, in some instances. The fact that unknown stage was so highly correlated with no appointment group perhaps signifies the importance of no appointment for those 70 and over.

6.5 Tests of Model Robustness

Once the final model was determined, tests of robustness could be performed. For this test, the 83 cases from the late appointment group were added to the two other appointment groups in turn, first to the appointment group and then to the no appointment group. A robust model would support the addition of this group to either group with few changes in significance.

Table 6.5 shows the results of adding the 83 cases with late appointments to the appointment group. The tables are quite similar. While high stage, high and unknown grade and no appointment*unknown grade were significant, age 70 and over

and the interaction of age ≥ 70 with unknown stage were not significant. In this case, having unknown stage was not significant in any subgroup.

Table 6.6 shows the results of adding the 83 cases with late appointments to the no appointment group. Again the results are similar to the final model except the variables, age 70 and over, unknown stage, and both interaction variables are not significant. Neither are any of the location variables.

In general, the final model fits the introduction of these late appointment cases, an indication that the model is robust, fitting more than the original population tested. Adding extra cases to the model has resulted in some changes in significance, which would be expected, but generally what is significant for the original set of patients is still significant for these patients. Therefore, it could be concluded that the model fits the general breast cancer population in Alberta. It may be applicable to other patient populations, especially other cancer patient populations.

6.6 Conclusion

The factors that affect survival from breast cancer are high stage, high grade, unknown grade, and local treatment. Unknown stage is significant to survival only in those age 70 and over. Having no appointment is significant to survival only in those who are also not graded. Therefore, appointment status is significant to breast cancer survival, but only in a particular subgroup of patients. Age 70 and over results in improved survival when other factors are controlled.

As unknown stage is highly correlated to the no appointment group, it is likely that those age 70 and over who have no appointment have an increased hazard, but the Cox survival regression analysis finds the unknown stage variable rather than the no appointment variable to be the significant interaction factor.

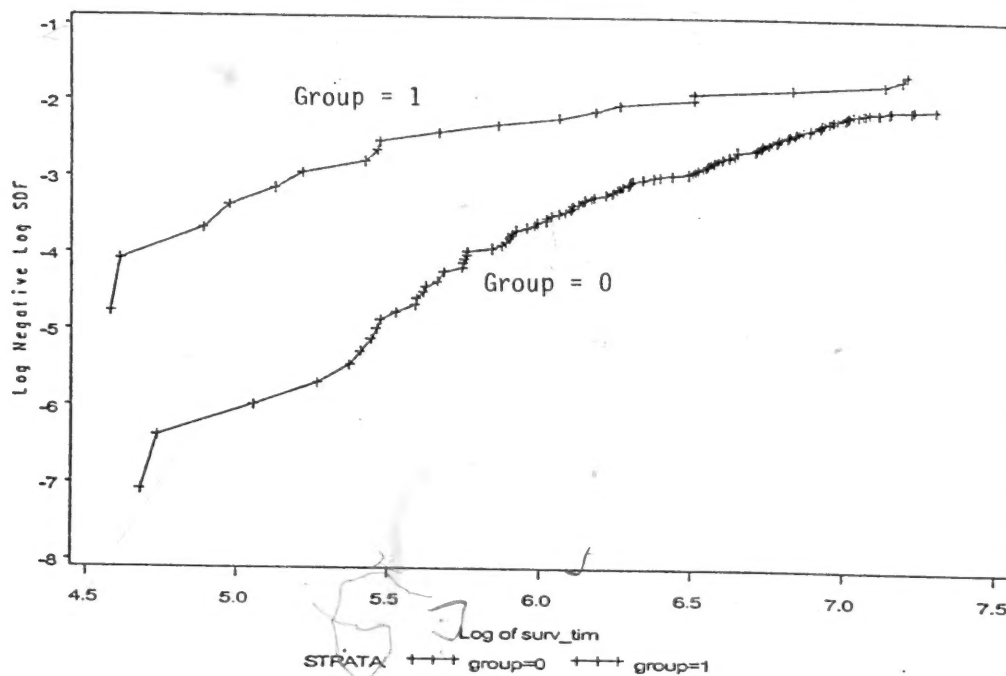
Location was not significant to survival in any of the controlled regressions. Marital status was not significant to survival from breast cancer in this study.

Although appointment group status is significant to survival in some situations, the variables that were significant to having no appointment, location and age group, have limited significance while marital status has no significance to survival.

Table 6.1: Univariate Kaplan-Meier Survival Analysis with Log Rank Test of Statistical Significance of Variables to Breast Cancer Specific Death.

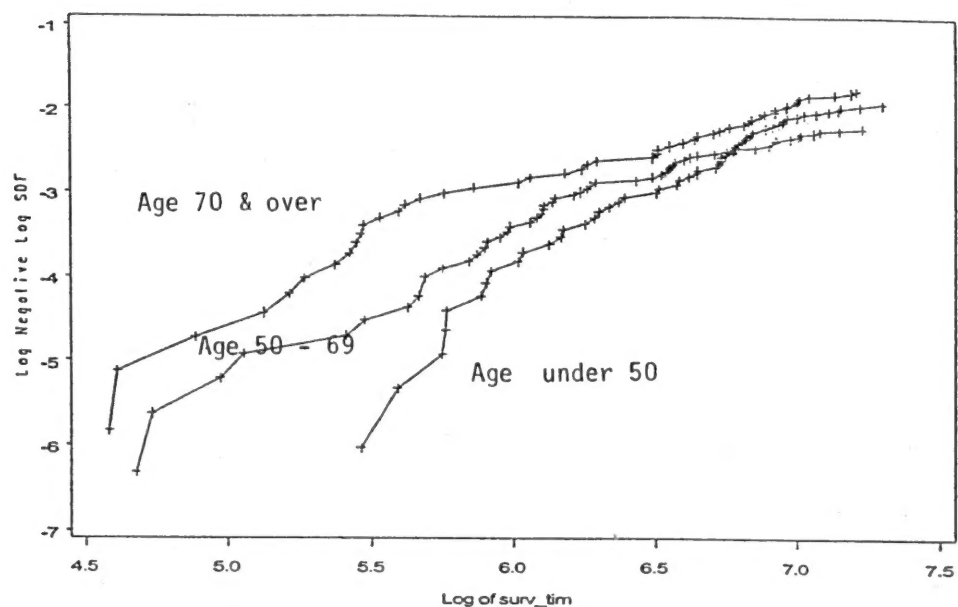
	Variable	p-value
Appointment Group	Appointment	reference
	No Appointment	0.031
Age at diagnosis	Age ≤ 50	reference
	Age 50-69	0.034
	Age 70+	0.054
Marital Status	Currently Married	reference
	Other	0.468
Stage	Low (I or II)	reference
	High (III or IV)	<0.001
	Unknown	0.008
ICD-O Grade	Low (I or II)	reference
	High (III or IV)	<0.001
	Unknown	<0.001
ICD-O Morphology	Ductal/Lobular	reference
	Not Ductal/lobular	<0.001
Location	Calgary	reference
	Edmonton	0.106
	Southern Alberta	0.081
	Central Alberta	0.256
	Northern Alberta	0.485
Local Treatment per Guidelines	Yes	reference
	No	<0.001
Systemic Treatment	Yes	reference
	No	<0.001

Figure 6.1: Log minus Log Survival Distribution Function for Appointment Group



Group = 0 - Appointment
Group = 1 - No Appointment

Figure 6.2: Log minus Log Survival Distribution Function for Three Age Categories



Age = 0 - Under 50
 Age = 1 - 50 - 69
 Age = 2 - 70 and over

Figure 6.3: Log minus Log Survival Distribution Function for Two Age Categories

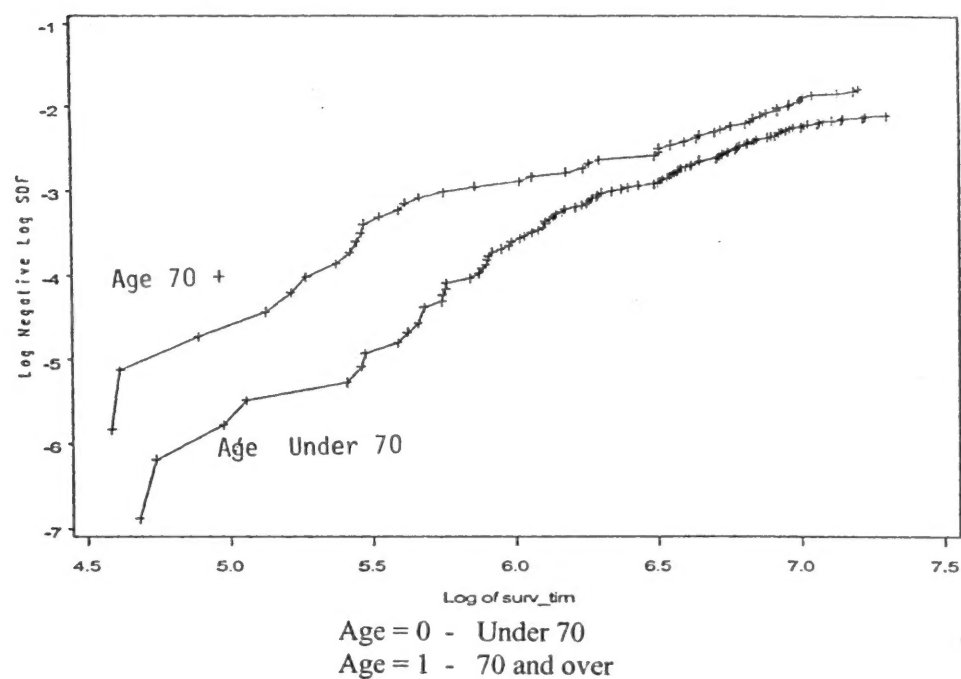
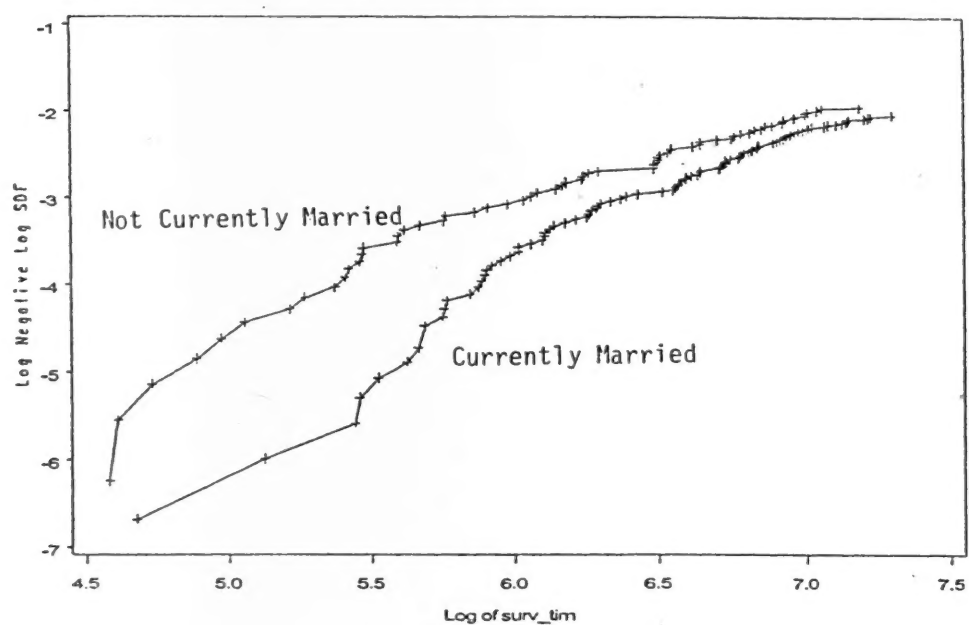
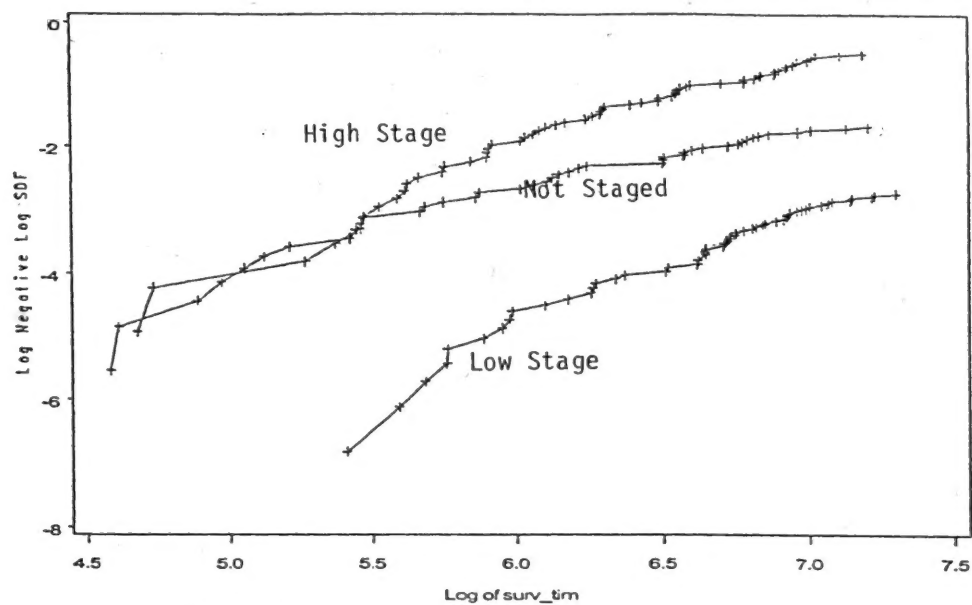


Figure 6.4: Log minus Log Survival Distribution Function for Marital Status



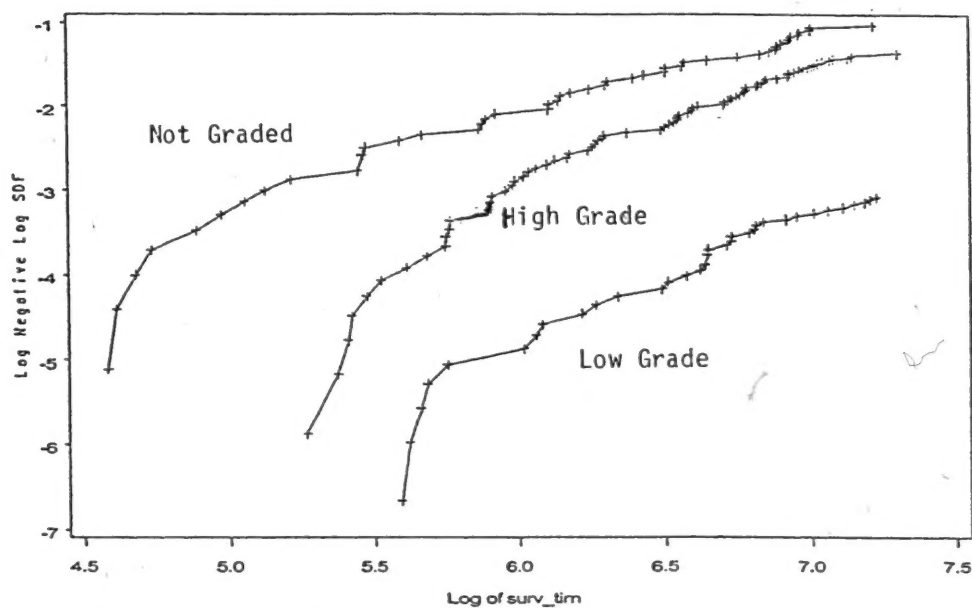
Marital Status = 0 - Currently Married
Marital Status = 1 - Currently Not Married

Figure 6.5: Log minus Log Survival Distribution Function for Three Stage Categories



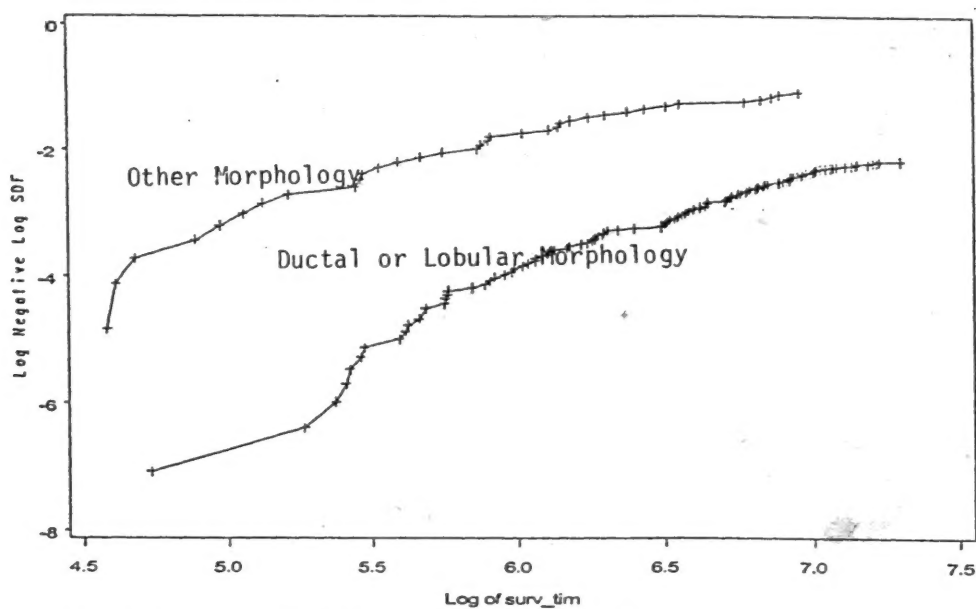
Stage = 0 - Low Stage
Stage = 1 - High Stage
Stage = 2 - Unknown Stage

Figure 6.6: Log minus Log Survival Distribution Function for Three Grade Categories



Grade = 0 - Low Grade
Grade = 1 - High Grade
Grade = 1.5 - Unknown Grade

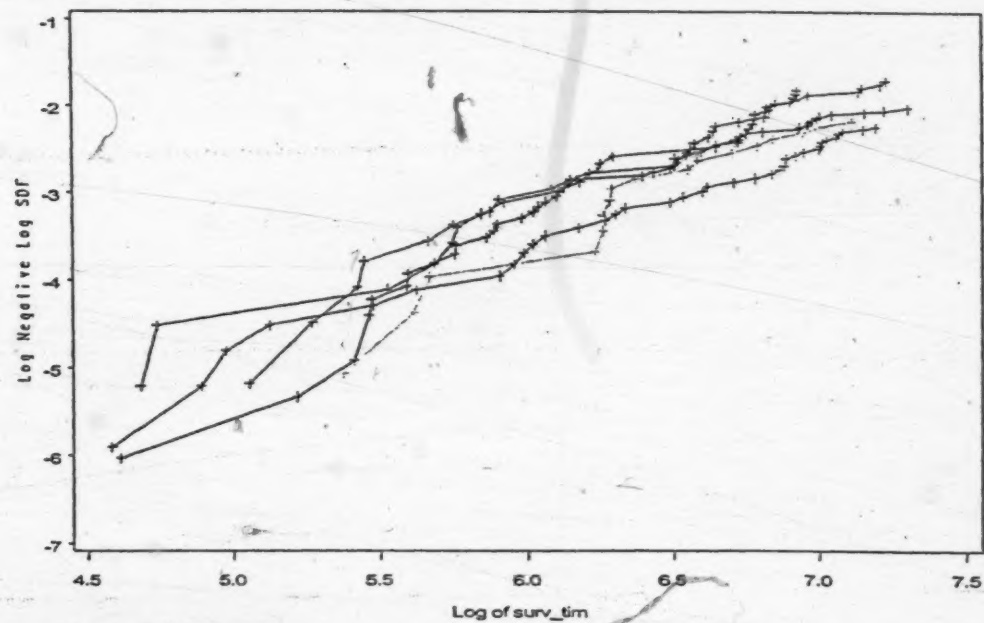
Figure 6.7: Log minus Log Survival Distribution Function for Morphology



Morphology = 0 - Lobular or Ductal

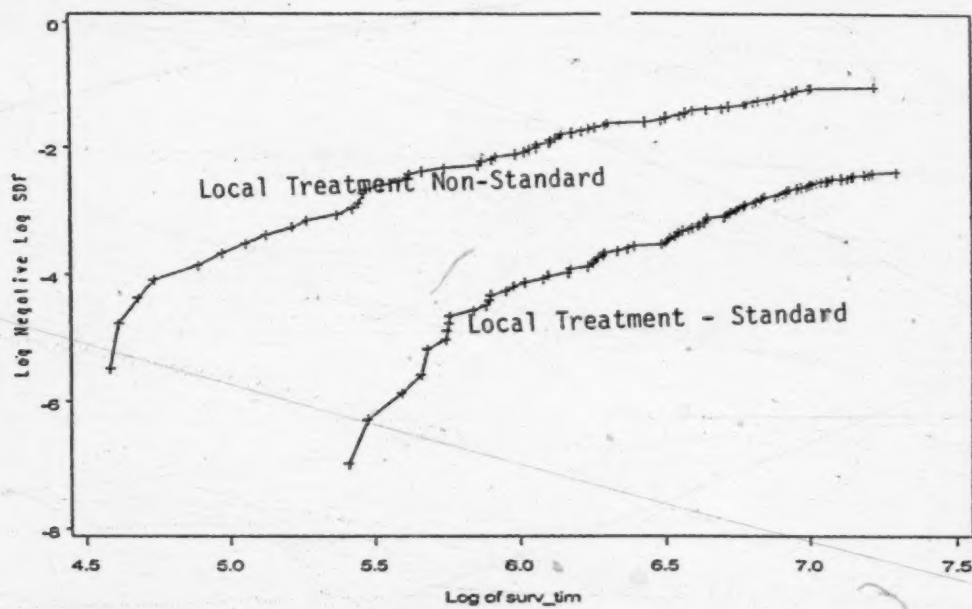
Morphology = 1 - Other

Figure 6.8: Log minus Log Survival Distribution Function for Location



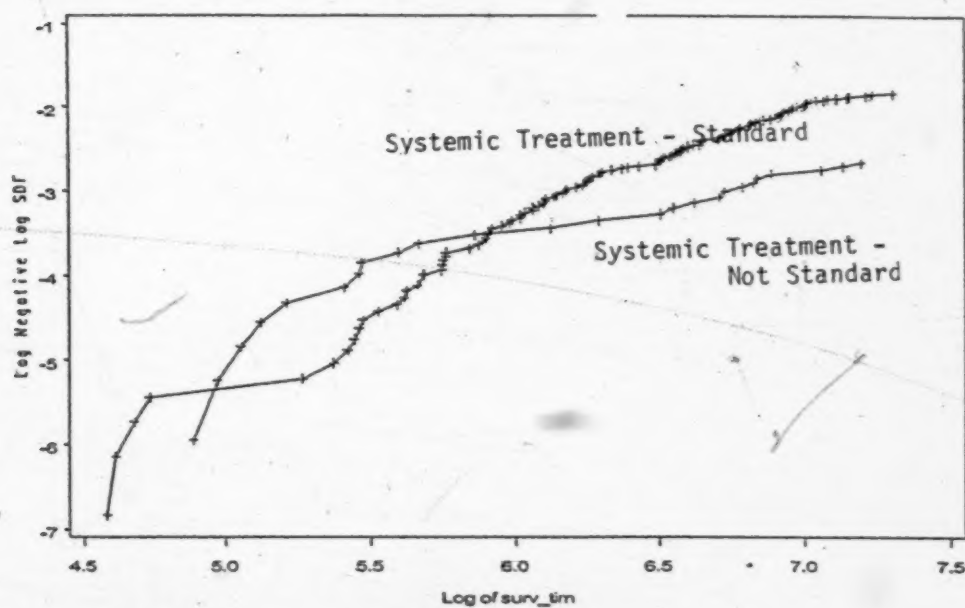
Location = 0 - Calgary
 Location = 1 - Edmonton
 Location = 2 - Southern Alberta
 Location = 3 - Central Alberta
 Location = 4 - Northern Alberta

Figure 6.9: Log minus Log Survival Distribution Function for Local Treatment



Local Treatment = 0 - Standard Local treatment
Local Treatment = 1 - Non-Standard Local treatment

Figure 6.10: Log minus Log Survival Distribution Function for Systemic Treatment



Systemic Treatment = 0 - Standard Systemic Treatment
Systemic Treatment = 1 - Non-Standard Systemic Treatment

Table 6.2: Univariate Cox Survival Analysis of Variables that Satisfy the Proportional Hazards Assumption.

	Variable	Hazard Ratio	Confidence Intervals	p-values
Appointment Group	Appointment	1		reference
	No Appointment	1.67	1.04 - 2.66	0.033
Age at diagnosis	<70	1		reference
	≥70	1.39	0.99 - 1.95	0.055
Marital Status	Currently Married	1		reference
	Other	1.12	0.82 - 1.54	0.469
Stage	Low (I or II)	1		reference
	High (III or IV)	6.76	4.92 - 9.30	<0.001
	Unknown	1.61	1.13 - 2.28	0.009
ICD-O Grade	Low (I or II)	1		reference
	High (III or IV)	2.68	1.97 - 3.66	<0.001
	Unknown	3.47	2.48 - 4.87	<0.001
ICD-O Morphology	Ductal/Lobular	1		reference
	Not Ductal/lobular	3.24	2.23 - 4.71	<0.001
Local Treatment per Guidelines	Yes	1		reference
	No	3.84	2.83 - 5.22	<0.001
Location	Calgary	1		reference
	Edmonton	0.74	0.51 - 1.07	0.107
	Southern Alberta	1.43	0.96 - 2.14	0.082
	Central Alberta	1.27	0.84 - 1.92	0.257
	Northern Alberta	0.84	0.51 - 1.38	0.486

Table 6.3 Initial Investigator Controlled Multivariate Model of Cox Survival Analysis, Breast Cancer Death Specific. N=1306. 83 Late Cases Not Included.

Variable		Hazard Ratio	Confidence Intervals	p-value
Appointment	Yes	1		reference
	No	1.29	0.72 - 2.31	0.394
Age	<70	1		reference
	≥70	0.95	0.65 - 1.38	0.770
Stage	Low (I or II)	1		reference
	High (III or IV)	5.54	3.76 - 8.16	<0.001
	Unknown	2.00	1.23 - 3.28	0.006
Grade	Low (I or II)			reference
	High (III or IV)	5.86	3.86 - 8.97	<0.001
	Unknown	3.99	2.46 - 6.48	<0.001
Morphology	Not Ductal or Lobular	1.00	0.65 - 1.56	0.986
Local	Standard	1		reference
Treatment	Not Standard	3.17	2.17 - 4.63	<0.001
Location	Calgary	1		reference
	Edmonton	0.97	0.63 - 1.51	0.899
	Southern Alberta	1.50	0.93 - 2.41	0.096
	Central Alberta	1.30	0.80 - 2.11	0.295
	Northern Alberta	0.81	0.50 - 1.44	0.478

Table 6.4 Final Investigator Controlled Model of Cox Survival Analysis, Breast Cancer Death Specific, with Interaction Variables Included. N=1306. 83 Late Cases Not Included.

Variable		Hazard Ratio	Confidence Intervals	p-value
Appointment	Yes	1		reference
	No	0.58	0.19 - 1.76	0.339
Age	<70	1		reference
	≥70	0.42	0.18 - .99	0.049
Stage	Low (I or II)	1		reference
	High (III or IV)	5.03	3.30 - 7.66	<0.001
	Unknown	1.49	0.81 - 2.74	0.205
Grade	Low (I or II)			reference
	High (III or IV)	5.64	3.64 - 8.75	<0.001
	Unknown	3.05	1.80 - 5.15	<0.001
Local Tmt.	Standard	1		reference
	Not Standard	3.13	2.15 - 4.56	<0.001
Location	Calgary	1		Reference
	Edmonton	0.93	0.60 - 1.45	0.744
	Southern Alberta	1.53	0.96 - 2.46	0.077
	Central Alberta	1.12	0.68 - 1.84	0.652
	Northern Alberta	0.76	0.43 - 1.35	0.353
Age*Stage	<70*low	1		reference
	≥70*high	2.64	0.95 - 7.37	0.064
	≥70* unknown	3.84	1.30 -11.29	0.015
Grade* Appointment	Low * Yes	1		reference
	High * No	0.76	0.13 - 4.38	0.756
	Unknown * No	3.73	1.09 -12.82	0.037

Table 6.5 Test of Robustness of Final Investigator Controlled Cox Survival Analysis,
83 Late Cases Added to Appointment Group.

Variable		Hazard Ratio	Confidence Intervals	p-value
Appointment	Yes	1		reference
	No	0.62	0.21 - 1.82	0.380
Age	<70	1		reference
	≥70	0.55	0.26 - 1.18	0.124
Stage	Low (I or II)	1		reference
	High (III or IV)	5.24	3.44 - 7.97	<0.001
	Unknown	1.56	0.87 - 2.78	0.134
Grade	Low (I or II)			reference
	High (III or IV)	4.98	3.292 - 7.53	<0.001
	Unknown	2.76	2.66 - 4.61	<0.001
Local	Standard	1		reference
Treatment				
	Not Standard	2.68	1.86 - 3.85	<0.001
Location	Calgary	1		reference
	Edmonton	0.944	0.61 - 1.46	0.795
	Southern Alberta	1.52	0.95 - 2.44	0.079
	Central Alberta	1.27	0.79 - 2.03	0.229
	Northern Alberta	0.77	0.43 - 1.36	0.48
Age*Stage	<70*low	1		reference
	≥70*high	2.14	0.84 - 5.47	0.111
	≥70* unknown	2.63	0.99 - 6.96	0.053
Grade*	Low * Yes	1		reference
Appointment				
	High * No	0.81	0.14 - 4.64	0.809
	Unknown * No	4.10	1.20 - 13.99	0.024

Table 6.6 Test of Robustness of Final Investigator Controlled Cox Survival Analysis,
83 Late Cases Added to the No Appointment Group.

Variable		Hazard Ratio	Confidence Intervals	p-value
Appointment	Yes	1		reference
	No	0.82	0.36 - 1.88	0.643
Age	<70	1		reference
	≥70	0.58	0.27 - 1.24	0.158
Stage	Low (I or II)	1		reference
	High (III or IV)	5.03	3.31 - 7.65	<0.001
	Unknown	1.69	0.95 - 3.01	0.077
Grade	Low (I or II)			Reference
	High (III or IV)	5.58	3.61 - 8.62	<0.001
	Unknown	3.21	1.90 - 5.40	<0.001
Local Treatment	Standard	1		reference
	Not Standard	2.77	1.92 - 4.01	<0.001
Location	Calgary	1		reference
	Edmonton	0.98	0.64 - 1.50	0.919
	Southern Alberta	1.53	0.951 - 2.45	0.078
	Central Alberta	1.36	0.85 - 2.18	0.203
	Northern Alberta	0.80	0.45 - 1.42	0.447
Age * Stage	<70 * Low	1		Reference
	≥70 * High	1.95	0.76 - 4.96	0.163
	≥70*Unknown	2.64	0.99 - 6.99	0.051
Grade * Appointment	Low * Yes	1		reference
	High * No	0.52	0.16 - 1.71	0.279
	Unknown * No	1.56	0.58 - 4.25	0.380

Chapter 7 - Discussion

7.0 *Introduction*

This chapter will review the results from the logistic regression and the Cox survival analysis and then discuss these outcomes in light of the literature on the topics. Results that are in keeping, and any that are not in keeping, with what is in the literature will be highlighted. The design of this study, using two databases in a retrospective cohort study will also be addressed as the third question of this study. Strengths and weaknesses will be presented. Areas for future research will be suggested.

7.1 *Review of Multivariate Results*

Table 5.8 shows the final logistic regression model of the factors that were significant for not having an appointment. Controlling for age group, grade, and morphology, the type of woman with invasive breast cancer who was least likely to have an appointment at an Alberta Cancer Board center was in an older age category (likely ≥ 70 but may have been between 50 - 69), not currently married, and more likely to have lived in Southern or Central Alberta. She was very likely to have an unknown stage and she was quite likely to have an unknown grade or an unusual morphology. Surprisingly, this hypothetical person was no more likely to be from the more sparsely populated areas of the province encompassing Northern Alberta.

Also, she was no more likely to be from a strictly rural location than those in the reference group (Calgary), even in the univariate analysis. As was discussed earlier, cases who do not have an appointment are not necessarily getting inferior care. The tests of model robustness (shown in tables 5.10 and 5.11), with the 83 late appointment cases added to either the appointment or the no appointment group, are

instructive. Adding these cases to the appointment group, which is where I think they belong, results in some modification of the odds ratios but only changes the significance of the middle age group, with this age not being significant. Adding these cases to the no-appointment group has very interesting results. Both age groups are significant. All of the locations outside Calgary, including Edmonton, are significant for no appointment. Looking at Table 4.16, it can be seen that while Calgary has only 7% of cases in the no appointment group (6% from the original group and 1% in the late group), every other location has over double that percentage, and Central Alberta has triple that percentage. This may indicate some problem in access to any appointment, rather than a problem of referral, in all areas outside Calgary.

The final Cox survival analysis, (see Table 6.4), revealed the factors that were a significant risk to survival specifically from breast cancer. They included high stage, high grade, unknown grade, and non-standard local treatment. Age 70 and over was a risk to survival only for those with unknown stage. Age 70 and over itself had significantly better survival. No appointment was significant only for those with an unknown grade.

Marital status was not significant to survival, even in univariate analysis. Age 50 - 69, analyzed only in the univariate Kaplan-Meier survival analysis, had a significantly better survival on the basis of the log rank test and looking at the survival graph. Location was not associated with an increased risk of mortality. Location in Southern Alberta had a trend towards an increased risk for survival. Adding the late appointment groups led to age 70 and over becoming non significant and had no effect on the location variables. The interaction variable age 70 and over*unknown stage became insignificant with the addition of the late group to either side of the appointment, no appointment spectrum. Unknown grade * no appointment became insignificant with the addition of the 83 late cases to the no appointment group. I

believe that the 83 late cases, if they belong anywhere, belong in the appointment group, where unknown grade*no appointment is still significant.

7.2 Which Group: Appointment or No Appointment?

The logistic regression analysis (table 5.8) established that certain groups of patients are less likely to have an appointment based on the demographic characteristics of age, location, and marital status. These significant factors will be discussed. Morphology and grade are disease factors that were used as control variables but will not be discussed in any detail. Stage, particularly unknown stage, must be discussed.

7.2.1 Age

Cases with age 70 and over had an eleven fold risk of no appointment, controlling for marital status, location, grade, and morphology, while those between 50 - 65 had a nearly three fold risk for no appointment. The majority of cases in the no appointment group (74%) were 70 and over.

The reasons given in the literature to explain why breast cancer cases age 70 and over are less extensively investigated and treated include: later stage at presentation, a higher rate comorbidity, the perception that these women either do not want treatment or that their life expectancy is very limited, and a lack of studies of women this age to justify the use of radiation or chemotherapy.

The last reason cited, that few studies exist for this age group, may be the primary reason that cases age 70 and over are not referred for an appointment. Studies of adjuvant chemotherapy and radiation therapy have not been done in this age group

and physicians are hesitant to apply therapy from a younger age group to an older age group. Only the clinical trials with tamoxifen even included women over 70. The clinical practice guidelines, which have analyzed the data in a systematic way, do not recommend systemic adjuvant chemotherapy for this age group except in unusual cases. This, in itself, would reduce the number of cases age 70 and over that are referred. Clinical practice guidelines also change. For instance, sentinel lymph node biopsy is now cautiously recommended in the revised Canadian Clinical practice guidelines⁴⁶. Without specific guidelines, treatment regimes will vary based on the individual experience, interest, and knowledge of the physician and the practices within institutions and in regions.

Long term studies that have followed cases as they grow older suggest that some practices may be harmful in older patients. Recent evidence indicates that radiotherapy reduces survival in older cases at low risk of local recurrence because of the effect on cardiovascular mortality⁴⁸. Even prior to the release of this study, this had been an issue in radiation for older women. Apart from the lack of studies of older cases, this apparent debate in the literature would encourage many physicians to follow a conservative approach to treatment.

The recommendations for axillary dissection are also open to interpretation. The clinical practice guidelines in Canada, Australia, and the U.S. all recommend axillary dissection^{39,41,45}, whereas those in the U.K. recommend axillary sampling³⁸. The Canadian clinical practice guidelines list age as a reason, along with comorbidity, for not doing an axillary dissection⁴⁵. In addition, some studies advocate axillary sampling instead of axillary dissection⁴⁹ and the newer Canadian guidelines do recommend sentinel node biopsy in certain circumstances⁴⁶.

Therefore, there is much diversity of opinion as to the best management of cases age 70 and over. This is the biggest reason why these cases are less often staged and/or referred for specialist consultation. At the time relevant to this study,

treatment of those age 70 and over needn't involve any more specialists than the surgeon, who can prescribe the tamoxifen if it is felt to be beneficial.

A second reason why older cases are investigated and treated less vigorously than their younger counterparts is because of comorbidity. Comorbidity is a significant predictor of non-breast cancer mortality^{68, 87, 88}. Studies have shown that while older cases do have a greater number of concurrent illnesses and more severe comorbidity⁶¹⁻⁶³, and that comorbidity in older patients limits the ability to obtain prognostic information and minimizes treatment options⁸, it is age itself that is associated with an increased risk of receiving non-standard investigation and treatment^{8, 59, 61, 63-66}.

Our cohort does not seem different than other populations. Comorbidity is not a measure that is available through the cancer registry data base but certainly, if one looks at cause of death for all appointment groups, the percentage of deaths caused by other than breast cancer increases from 5% in the timely and 0% in the late appointment groups for those under 50, to about 50% of deaths for those age 70 and over, in all three appointment groups. Comorbidity, more prevalent in the aged, was evident in all three appointment groups and may have been the reason why some cases in the no appointment group were not referred for further investigation and treatment. However, it would be most unlikely that comorbidity accounts for all of the cases that are in the no appointment group especially when one considers that other authors have tested this theory and found that chronological age is the more likely reason for no appointment. Less than standard treatment of older patients, controlling for comorbidity, has been found to contribute to poorer survival¹⁰³ and likely contributes to the poorer survival in the no appointment group for breast cancer only deaths.

Interestingly, one researcher has suggested that the development of breast cancer in a case will accelerate the course of other pathological conditions. As a result, the risk

of death from these other conditions may be greater after breast cancer develops⁶⁸. If this is true, than one might expect an even greater death rate in the no appointment group from causes other than breast cancer, if all of these cases had no appointment because of comorbidity.

A third reason postulated why older women are less often referred to an oncologic service for treatment is that older women may be more likely to present at a later stage. This could be for several reasons: older women are not actively screened, older women may not know the presenting signs and symptoms, or older women may have too many other concurrent illnesses to notice a breast cancer. However, several studies have found that older women do not present at a later stage than their younger counterparts^{59, 61, 63, 67, 68}. Some of these same authors have also noted that older women are less often staged^{8, 60, 61}.

The results of this study are therefore, not exceptional. In this study, 70% of all patients (in the appointment, late, and no appointment groups) were low stage (I & II), 10% were high stage (III & IV), and 20% were unstaged. The percentage of patients in the age group 70 and over, who were high stage (9%), was quite comparable to the 11% of those under 70. However, 40% of those age 70 and over were not staged compared to just 14% of those under 70. Comparable to the other studies noted above, the older patients in this study were less often staged than younger ones whether or not they had an appointment. In the no appointment group, the majority were in the oldest age group, none had an appointment, and nearly 90% were not staged. Whether the cases in the no appointment group actually presented at a later stage is unknown but it is unlikely considering the literature. Had they been at a later stage, I would have expected a greater percentage to also have a high grade, as high grade and high stage are often correlated. In fact, 61% of cases in the no appointment group were low grade and 12% were high grade, the remainder were unknown. In the appointment group 60% were low grade and 29% were high grade, while in the late group, 68% were low grade while 25% were high grade. If all the unknown cases in the no appointment group were high grade, which is very unlikely, then the no

appointment group would have 39% high grade at most, which is more than the other groups but not double or triple the rate.

Another reason why I think that the no appointment group had no more late or high stage cases, is that if many more had been late stage, one would have expected even more breast cancer specific mortality than there has been, by now. About 17% of the no appointment group have died from breast cancer, while 12% of the appointment group have died from breast cancer. If there were a much higher percentage of high stage cases in the no appointment group, one would have expected many more breast cancer deaths. 17% compared to 12% is not too bad when one considers that these people had no referral for consultation and were not at all aggressively treated.

A last reason to think that the unstaged cases among the older women were likely low stage is the effect of the clinical practice guidelines. The 1998 Canadian guidelines do not always recommend axillary lymph node dissection if the results are not going to change the treatment strategy and if no further investigations are contemplated. If a patient is clinically node negative, that is, low stage, there may be no point in doing the lymph node dissection. Therefore, perhaps some of the older patients who have no stage, were not investigated because they were clinically low stage and the treatment would not have changed with a lymph node dissection. It is important to keep in mind here, that more of the no appointment cases were clinically staged, at least, but the information never reached the cancer registry.

A final reason why older persons are not investigated or treated as aggressively as younger persons is the feeling that they will die soon anyway, so that aggressive treatment would not be beneficial and may cause more harm. This seems reasonable as the physicians first rule of practice, 'primum non nocere', is invoked. There is also the thought that older persons do not want to be burdened with the side effects of treatment. In an analysis of patient's perspectives though, it was found that older

patients do want a full range of therapeutic options and patient's list side effects infrequently as a reason for not choosing treatment. They credit their physician's recommendation as the most frequent reason for not choosing adjuvant chemotherapy⁷⁰. Their physician has not recommended adjuvant chemotherapy. Other studies have found that physicians spend less time with older patients and involve them in decision-making about treatment options less often⁶⁹. Although our study was not designed to address these questions, there is a likelihood that some of these findings applied to our no appointment cases. Just the fact that 75% of the no appointment cases were age 70 and over is some proof of this.

In conclusion, the results of our study, with many more cases age 70 and over being non-referred for an appointment, are not unusual. It is likely that some were not referred because of comorbidity and it is also likely that some were not referred because referral was not recommended by their physician. It is unlikely that many were not referred because of presentation at a later stage. It is most likely that many older cases were not referred because the clinical practice guidelines do not recommend aggressive treatment or investigation for older women and there are very valid questions as to the advantage of axillary node dissection or radiation therapy in the older patient. Why would physicians recommend toxic treatments for older patients when suggested effective treatment, ie. tamoxifen, is available that has few side effects and does not necessitate extra trips to see other specialists?

The problem of how to treat the elderly is growing. Breast cancer has a higher incidence in older women and the percentage and absolute numbers of older women is growing. Therefore, there should be clinical trials that focus on the elderly population so that treatment can be based on objective measures. In these trials, quality of life, functional status, and effect on comorbidity should be measured. Disease specific as well as overall survival needs to be assessed.

7.2.2 Marital Status

In both the univariate and the multivariate analysis, not currently married cases were statistically significantly more likely to be in the no appointment group. One would think that this was simply an association with age but age was a controlling variable. The effect of marital status was present whether age was entered as a three level categorical variable (odds ratio 8.98, confidence intervals 4.85 - 16.62) or as a continuous variable (odds ratio 7.28, confidence intervals 3.89 - 13.63).

Other studies have found similar seeming bias against not currently married women. Goodwin's very large study of over 25,706 cases of any epithelial cancer in New Mexico between 1969 and 1982 showed that not currently married cases do worse on every level. They are diagnosed at a later stage, they are less likely to be treated, and they have poorer survival⁷². Marital status is one of a number of social factors which influence the management of patients with breast cancer, especially for older women. Generally, being currently married has a positive influence on the decision to pursue axillary lymph node dissection, specialist consultation, and receive either hormonal or chemotherapy⁶⁶. Other investigators have also commented on the differences in treatment between currently married and not currently married cases⁶⁹.⁷³ Currently married persons live longer, with lower mortality for almost every major cause of death.

More recently, Du and colleagues, in a study of about 130,000 early cases of breast cancer between 1983 to 1993 through Seer Registries, have found that not currently married cases are less likely to receive either axillary node dissection or radiation. If the clinical stage is node negative, these cases are less likely to receive systemic treatment¹⁰⁴.

Marital status is one of a number of social factors which influence management of patients with breast cancer, especially in older women. Older women who are not currently married are more likely to be living alone⁶⁹. They may have difficulty with transportation. They may lack social contacts and they may not have a mentor with whom to discuss investigation and treatment options. In addition, if they do not have a mentor, they may be even more dependent on their physician's recommendations. At the same time, the physician's recommendations may be influenced by the fact that the woman doesn't have the apparent social support necessary to undertake extensive investigation or treatment. Alternatively, a physician may spend even less time with a lone older patient than a currently married patient and her husband.

The reasons for the influence of marital status are not clear but it is apparent that marital status has a significant effect on the investigation and treatment of breast cancer. The reasons for this effect deserve further investigation. In this study, at least, being not currently married has no effect on survival. This either reflects the short time-frame of this study in terms of survival, or the likelihood that these cases are well cared for even if the care is different.

7.2.3 Location

This study found a statistically significant effect of location on appointment group status. Patients in Southern Alberta (odds ratio = 2.5, 95% confidence interval = 1.3 - 4.9, $p=0.007$), and those in the Central Alberta (odds ratio = 2.5, 95% confidence interval = 1.2 - 5.0, $p=0.011$), were more likely to be in the no appointment group than patients in Calgary, Edmonton, and Northern Alberta. These effects were controlled for age, grade, morphology, and marital status but not for physician, hospital, or regional factors that have been shown to influence the investigation and

treatment of breast cancer. These findings are in keeping with the literature on this topic^{75, 81, 105-107}.

In an Ontario study, it was hospital characteristics, and not regional variation, that predicted higher use of breast conserving surgery. The salient hospital characteristics included participation in clinical trials, medical school affiliation, and the availability of radiation therapy¹⁰⁸. Teaching hospitals have higher compliance with accepted investigation and treatment standards than non-teaching hospitals. The salient hospital characteristics noted in the literature certainly describe the two major metropolitan locations in the present study. Edmonton and Calgary are both characterized by the presence of medical schools, participation in randomized clinical trials, and available radiation therapy. These hospital characteristics may have something to do with the fact that Calgary formed the reference and Edmonton was not significantly different from that.

Physician differences, including surgical specialization in breast cancer and higher breast cancer caseloads, have also been found to underlie differences between geographic regions. Patients treated by a surgeon who either specializes in breast cancer or has a large volume of breast cancer patients are more likely to find themselves referred to specialized treatment centers¹⁰⁹. Large volume practices are usually situated in larger urban centers which is in line with our findings.

Physicians also reflect different viewpoints on the value of therapies. There is some question of the value of radiation therapy for all patients after breast conserving surgery. This is likely linked to studies such as the Early Breast Cancer Trialists' Collaborative Group⁴⁸, which warns that overall long-term survival may not be as good for older cases or cases that are very early, who receive radiation therapy with breast conserving surgery. This may be the case with surgeons in Southern Alberta. There may be other unknown reasons also, but in Southern Alberta, although cases are just as likely to receive some type of systemic therapy as cases anywhere else in

the province, they are much less likely to receive radiation therapy following breast-conserving surgery. Tables 4.22 and 4.23 illustrate the difference in local and systemic treatment between the five regions in Alberta. Apparently, in Southern Alberta, although patients are being referred to specialist treatment centers less often, they are certainly being treated by their local physicians.

Northern Alberta, which is more remote and sparsely populated than the rest of the province, did not differ from the reference, Calgary, as far as appointments were concerned. The North had proportionately fewer no appointment cases than either Central or Southern Alberta, which both have, or are closer to, treatment facilities. In an American study, Farrow⁷⁵ attributed significant regional differences in the use of breast conserving surgery and accompanying radiation therapy to unidentified regional factors in different areas of the United States. There may be some regional factors in Alberta that influence how patients are managed. It would be interesting to know what the factors are in Northern Alberta that decreases the likelihood of no appointment compared to Central and Southern Alberta.

One study found that rural location and distance does not have to affect the quality of care for patients¹¹⁰. This certainly seemed to be the case for Alberta. There was no significant difference between the care of strictly rural people and that of more urban folk. If living far from a treatment center was significant to treatment, one might expect cases from more remote locations of the province to elect to have a mastectomy instead of breast conserving surgery so that they would not have to attend daily radiation therapy for six weeks. If this were the case, then the percentage of patients having breast conserving surgery from these areas would likely be decreased compared to the two major urban areas.

Table 4.22 shows the differences between regions for cases receiving standard local treatment. Edmonton had the highest level of accompanying radiation following breast conserving surgery at 90% and, due to this factor, it also had the highest level

of standard local therapy. The rates of radiation following breast conserving surgery for Central and Northern Alberta were comparable to that of Calgary at 83%. Southern Alberta had the smallest percentage of radiation following breast conserving surgery, 44%, and therefore, the smallest percentage of cases receiving standard local therapy. From these numbers, it seems apparent that distance from a radiation therapy facility may not be as much of a factor in treatment decisions. Especially in Northern Alberta, distances can be a great length but this doesn't seem to effect treatment choices to any degree that would make them much different from those in the major urban centers.

7.2.4 Stage

In this study, unknown stage and having no appointment were highly correlated. This could be expected from a review of the literature, as those least likely to be referred are also those least likely to be staged^{8, 60, 61}. Stage is an extremely important variable in analysis of treatment patterns and in survival analysis. However, with nearly 90% of the no appointment group having an unknown stage, stage lost its validity as a control variable in the multivariate analysis of appointment group status. Most studies would drop subjects with unknown stage. In this study, dropping these cases would result in the loss of too much information. These are perhaps the very cases that should be included in studies looking at the influence of various variables on treatment choices and referral to specialized cancer facilities. This study was able to include the unstaged cases by assigning a value to unknown stage so that they were not rejected from the statistical analysis program. Not including stage in the logistic regression to determine variables important to appointment group could be significant. However, the main outcome of the logistic regression was appointment status, not treatment or survival. When unknown stage is viewed as an outcome variable in the same sense as no appointment, then differences between age groups, marital status, and location in the proportion of unknown stage cases reinforce this

view rather than indicating that there was a real difference between the percentage of high and low stage cases. In fact, the percentage of high stage cases was the same for currently married and not currently married, similar for the five different regions, and also very similar between age these proportions.

Unknown stage, like the no appointment group, is an outcome variable according to much of the literature. It is also predictive of poorer survival. Unknown values for variables are often thought to be useless. In this study, unknown stage was useful because it mirrored the literature, it was a valid outcome in a parallel logistic regression (Table 5.12), and it was significant to survival for those 70 and over in the final Cox survival analysis (Table 6.4).

The variables that were significant to breast cancer specific mortality included high and unknown grade, high stage, non-standard local treatment, age 70 and over in cases who were of unknown stage, and no appointment group in cases that were not graded. Marital status was not significant to survival. Location in Southern Alberta trended to significance. Age 70 and over gave a survival advantage in the multivariate model. No appointment group was not significant outside of the interaction variable. High grade and high stage are known risk factors for breast cancer and will not be discussed further than to say that our study reflects that these factors are both clinically and statistically significant.

Local treatment was used as a control variable in this study. Systemic treatment was not used because it did not satisfy the proportional hazards assumption. There was no way of determining if either treatment was adequate other than knowing that cases received either standard local treatment, consisting of breast conserving surgery plus radiation or mastectomy, or some form of systemic therapy, either chemotherapy or hormone therapy. Cases in the no appointment group could receive both standard local and standard systemic treatment without referral so that treatment could be used as a control variable in the survival analysis. Although this study was not an assessment of treatment and the treatment variable available does not reflect all treatment, it was thought that treatment could still be a valid control variable and should be used.

If one stratifies by systemic treatment as a control measure, for those that receive systemic treatment, high and unknown stage and grade and non-standard local treatment are significant to survival. For those that do not receive systemic treatment, high grade, high stage, non-standard local treatment, and no appointment * unknown grade are significant to survival. Unknown stage is significant overall, for those who

have treatment, and not just for those age 70 and over. The fact that non-standard local treatment is significant for those not receiving systemic therapy also points to unknown stage. These are people who had breast conserving surgery with no adjuvant radiation and no adjuvant systemic therapy. It is most likely that these were clinically node negative with small tumours. Therefore, it was decided that systemic treatment was not necessary and also radiation wasn't done. Likely, a significant percentage were pathologically node positive, and would have benefitted from systemic therapy at least, but their true node status was not known.

The variables of interest to this study will be discussed.

7.3.1 Group

No appointment group was only significant to poorer survival in those who were not graded (hazard ratio 3.73, 95% confidence interval 1.09 - 12.82, $p=0.037$). Therefore, our second thesis question, 'does appointment group influence survival?', is answered in the affirmative. It does influence survival in those who are not graded. In those who are low grade, appointment group is not significant, while in those who are high grade, appointment group probably makes no difference to the already poor survival outcome.

These results reflect what has been found by others: if breast cancer, for whatever reason, is not appropriately managed, a poorer survival may result. Our no appointment group reflects some aspects of management that may be missing, and in some cases, the survival is affected.

7.3.2 Stage

Unknown stage was significant only in those 70 and over. Because unknown stage is like a proxy for no appointment group, the finding that it is significant for poorer survival in those 70 and over is important because it acts as further proof that under-investigation and minimal treatment are significant to survival. We chose appointment group as our outcome variable for testing what influences appointment status. Others have referred to inadequate staging as another sign of less appropriate management. Our study confirms that. Similar to our findings, Lash found that less than definitive prognostic evaluation (which included axillary dissection and estrogen receptor status) was associated with an adjusted relative hazard of recurrence of 1.7 (95% confidence intervals, 1.0 - 2.7) and an adjusted relative hazard of mortality of 2.2 (95% confidence intervals, 1.2 -3.9) ¹¹¹.

It is interesting that the unknown stage was only significant for age 70 and over. For younger cases, unknown stage would have had an opposite effect or the interaction variable would not have been significant. Unknown stage in age under 70 was not hazardous. Perhaps those under 70 who had unknown stage had such early disease that their outlook was excellent without much investigation and treatment. Perhaps those under 70 whose stage was unknown had screen detected disease, which is less likely to have spread to the regional nodes and in the view of some investigators, may never have caused any problem in the life of the woman, had it been left alone ¹¹².

There is a strong correlation between unknown stage and age 70 and over, as it is mainly cases who are in this age group who are not staged. The non-significance of the two variables, age group and appointment group, is made up for by the significance of the unknown stage variable.

7.3.3 Age

With all of the variables in the final model including local treatment and the interaction variables, age 70 and over was just significant to better survival! Age 70 and over as a product term of unknown stage was significant to poorer survival. This is interesting, as generally age itself is associated with poorer survival from all causes. In fact, the Charleson comorbidity index incorporates age into the score, so that an 80 year old with no other comorbidity would still have a higher comorbidity score, and consequent poorer survival, than a 60 year old or a 40 year old⁸⁷. This attests to the fact that age is usually associated with poorer survival.

In our study, only a subset of those 70 and over were more likely to die of breast cancer. Those who are age 70 and over who are investigated and treated for breast cancer do better than younger cases. At this point, it seems that people age 70 and over could really benefit from a standard of treatment.

Of course, the subjects in this study age 70 and over did die of other causes more often than the younger group, but their breast cancer did not have a worse prognosis for them than younger cases except in unstaged cases. Not being staged is not a characteristic of disease but a characteristic of management. If those aged 70 and over are managed in the same way as younger patients, with adequate investigation and treatment, then this study shows that their breast cancer mortality need be no more than that of younger patients.

A caution must be noted. First, age 70 and over having improved survival, controlling for other variables may be an artefact of the normal distribution of the population and just happened to occur by chance here. Secondly, the time elapsed for measuring survival is too short to measure the effects of either local or systemic

therapy. Third, deaths from other causes were more common in the oldest group and it is these deaths that need to be assessed in any study of treatment in the aging. Recent results from the Early Breast Cancer Trialists Collaborative Group indicate that radiation in older individuals can result in poorer survival from cardiac causes than is made up for by improved survival from breast cancer. These results do not become apparent until years after the initial diagnosis and treatment⁴⁸. Of course, they may change with new and better methods of delivering radiation and protecting the heart. Studies of this would need to be very long standing and there is evidence that if modifications of delivery of radiation are made to protect the heart, radiation therapy is beneficial to survival as well as to control of the cancer at the local level

113

7.3.4 Marital Status

Marital status was statistically significant to appointment group status but not to survival in any analysis. Table 7.1 gives a cross tabulation of marital status by age category, unknown stage, unknown grade, and group. Three times as many not currently married as currently married cases were age 70 and over, over two times as many were unstaged, about one-third more were not graded, and nearly ten times as many were in the no appointment group. Because these variables were all part of the interaction variables that were significant to survival, it is quite likely that marital status, via this indirect route, may also be significant to survival. There would be more not currently married cases that were age 70 and over and also not staged, a significant combination associated with poor survival. There would also be more that were ungraded with no appointment, another combination with poorer survival. Therefore, while marital status was not directly related to survival, management on several levels of cases that were not currently married was associated with a decreased survival.

The reasons for the differences in management between those who are currently married and those who are not are not known. Other studies have noted the difference in management and survival between those who are currently married and those who are not^{72, 104}.

An awareness of this apparent bias represents an opportunity to further investigate the reasons for these differences and whether they do result in increased mortality.

7.3.5 Location

Location in Southern Alberta was nearly significant in the final model.

Table 7.2 gives a cross tabulation of location by age category, unknown stage, unknown grade, and group, the factors that were important as interaction variables in the survival analysis. The population of Southern Alberta is older than the other four locations. Both the general population of women in this location, and the breast cancer specific population, is older with a higher percentage of women age 70 and over. The percentage of cases in this location who were age 70 or older was 35% compared to the provincial average of 27%. None of the other locations had any more than 27% of breast cancer cases age 70 and over. The percentage of all women in this location who are age 70 and over is 10% compared to 8% for the whole province. There are more cases age 70 and over in Southern Alberta who are not staged (see Table 7.2). The combination of a higher percentage of cases age 70 and over and a higher percentage of unstaged cases was significant and very present in Southern Alberta. Therefore, the location may still have some relevance to survival even if the location variable itself was not statistically significant.

The appointment group is only significant in the ungraded cases. Again this combination is more likely to be present in Southern Alberta so in another way location seems to be relevant to survival.

Another interesting factor is treatment patterns. As tables 4.22 and 4.23 illustrate, in Southern Alberta there was significantly less local therapy considered standard, because there was less radiation after breast conserving surgery although there was as much treatment with systemic treatment as in any of the other locations in the province. The results of this study indicate some importance of standard local therapy to survival. Standard local therapy, when it was tested, was statistically significant to survival in a multivariate model. In addition, the location with the highest percentage of cases receiving standard local therapy, Edmonton, had almost statistically significant better survival than the rest of the province, while Southern Alberta had statistically significant poorer survival until interaction terms were introduced into the model. This parallels the results of a review by Dodwell, in which it was shown that radiotherapy to gain local tumour control also had positive effect on long term survival¹¹³.

7.4 Database Analysis

The third question that was asked in this thesis was whether using databases would allow a determination of whether there are differences in treatment patterns, particularly based on location of residence, and whether these differences led to a difference in survival. The answer to the question is a definite yes. We were able to establish patient appointments in one data base and merge the data with another data base from which we derived most of the patient and tumour characteristics discussed. In this institution, we believe that this is the first time that this has been done. We were able to develop a picture of what treatment was like in all areas of Alberta in 1997. Some of the results were surprising.

The databases used are both huge and it is a credit to the data managers that the information is kept in a retrievable form as a permanent record. Because some areas of the province seemed to have less referrals for appointments, we wondered if the appointments system was working in those areas at that time. Two pieces of evidence convinced us that they were. First of all, if the appointments were not accurately recorded on the database for those two areas of the province, would the regions have selectively recorded only the appointment data for currently married women or women under 70? Apart from the regions, not currently married women and women age 70 and over seemed also not to have appointments. It would be unusual for a system to not record appointments just for these two groups. The second bit of evidence that suggested the women in the no appointment group really had no appointment was just a frequency of appointment type and appointment status. 118 women had neither. 1 woman did have an appointment, in 1994, for another investigation. We concluded that we did have all of the appointment data. We also concluded it was good data because it was in logical order. For instance, the appointment was not prior to the diagnosis. The registry data, already discussed, was accepted as complete and of high quality.

7.5 Strengths and Limitations

There are several strengths and some limitations to this study that should be kept in mind in interpreting the results. Strengths and then limitations will be discussed in turn.

7.5.1 *Strengths of the Present Study*

The Alberta Cancer Board is a province wide organization, and as such, has data on all cases of cancer within the province because of the Alberta cancer registry mandate to collect data from all cancer cases. Therefore, the thesis was population based and one can be reasonably sure that almost every case of female breast cancer in the province in 1997 was captured in the study. This minimizes the bias from selection, as all cases, within certain preset guidelines, were selected. The results are more generally applicable than a hospital based study would be. In addition, the study size was big enough to allow some conclusions to be made.

The data from both databases, registry and appointments, was fairly complete and accurate. It was not collected for the study, which could introduce a bias, but it was sufficient for use by the study. Working with existing data removes a further chance for bias that might exist if an investigator must also collect the data.

Another strength of this study was that it was efficient for the collection and analysis of information on a large number of cases. More cases would not have extended the time necessary to complete this study, because the study was not based on the analysis of individual charts. Not only did databases provide the information, superior statistical software (SAS) was used to store database information and perform the statistical calculations necessary for analysis. Within this economic design, an investigator could go back and do a more expensive nested case-control study using charts instead of the database, or even contacting patients, doctors, and hospitals. Only cases-eg the not currently married, and controls would be studied so that the whole cohort would not need to be reviewed. This might be useful to determine the reason why marital status or age was significant to appointment group. Follow-up for survival status was automatic as the registry routinely links to vital statistics for vital status information. No cases were lost to follow-up in this study, because of this regular linkage.

7.5.2 Limitations of the Present Study

The results of this study must be taken with caution. Not all relevant information was available from the databases. There is no information on co-morbidity, functional status, hormone receptor status, tumour size, or number of affected lymph nodes from the Alberta Cancer Registry. These variables have a significant influence on treatment choices and survival status.

Treatment information may be limited on patients not having an appointment. They may have received hormone treatment without this information being available to the registry. This would tend to dilute the results, as survival would be better for these patients than predicted, which is perhaps why appointment group itself had no direct effect on survival.

In addition, there was no access to information on why patients were treated or were not treated. Patient and physician attitudes were not accessible. It is therefore, impossible to say why this happened.

A second area of weakness is the lack of hospital and physician information. There is no data about university or medical school affiliation, involvement in clinical trials, or volumes of breast cancer cases per year.

7.4 Areas for Further Research

Considering that the burden of treatment of older patients is going to increase and that these patients appear to want treatment opportunity that is equal to that of younger patients, it appears incumbent to address the problem of treatment of elderly patients. The benefits of treatment with either radiation or cytotoxic chemotherapy should be addressed. The benefit of axillary node dissection needs to be addressed. This would

aid in providing standards of treatment that are not presently available. This is of great importance for the future when both the proportion and absolute numbers of women over 70 will be increasing⁵⁷.

Comorbidity status is both clinically and statistically significant to treatment options and to survival. Because of the importance of this variable, there are some who argue that cancer registrars should be trained to retrieve this information from the chart⁸⁸. Piccirillo advocates an integrated stage and comorbidity variable as having more meaning than simply stage alone. It would be worthwhile to assess the possibility of entering comorbidity data into the cancer registry database. As the population ages, this information becomes more important than it is now. In the present study, the presence of a comorbidity score may not have been informative about the no appointment group. Like the missing stage information, it is probable that comorbidity information would not ever reach the registry for patients that are not referred in for an appointment. Having accurate information about both co-morbidity and stage would be of value to any of the clinical trials that are ongoing and also to assess the value of screening programs.

In relation to this, many cancer registrars are able to stage breast cancer and other cancers very quickly by reading the stage information available on a chart. Having the UICC or TNM stage would be a more valuable variable than the present clinical stage, which is a non-standardized, narrative, description of stage which must be transformed into a usable form by any researcher. Studies of the feasibility of providing UICC or TNM staging on the registry record could be worthwhile.

Age and perhaps location are somewhat understandable to appointment group status. However, it is not intuitive that marital status should be significant to appointment group status. What are the factors that are present here? These are unknown and do qualify for further study. In addition, because marital status is associated with factors

that are significant to poorer survival, these observed relationships should be further pursued. Are the factors related to co-morbidity and functional status, living arrangements and transportation issues, or physician - patient communication problems? Is this study simply a reflection of the fact that physicians make the decision to refer a patient for an appointment on many variables that were not available to this investigator? Perhaps appointment group status reflects an overall poorer prognosis for an individual case, and the physician, rather than causing a poorer outcome by not referring, has already predicted a poorer outcome and thinks that referral would not be beneficial. The question why this is more common for women in two locations of the province and women who are not currently married still begs for answers and is worthy of future study.

Considering location, non-referral is somewhat understandable. What is interesting is that women from the more remote locations in Northern Alberta were no less likely to be referred than women in Edmonton or Calgary. What are the factors contributing to less referrals from the Southern and Central parts of the province? What is happening in Northern Alberta that contributes to a similar proportion of referrals as Edmonton or Calgary?

In summary, this study has identified groups of women with breast cancer who were less likely to be referred for specialist care by an oncologist. Why these women are not referred can only be conjectured from this analysis. Other studies could determine more accurately why these women are not referred. Death from breast cancer is influenced by stage, grade, age in those with unknown stage, and no appointment group in those with unknown grade. Because no appointment group and unknown stage are highly correlated, it is suggestive that appointment group, and its determinants, are likely important to survival. This suggestion should be further developed. Lastly, the design of this study, using two databases, is innovative and efficient. Data is collected by well-trained and experienced personnel who are not collecting the data for the study and are therefore, not biased. The information, while

lacking in some areas, is generally complete and of very high quality. The databases are automatically updated for each case and death, in particular, is not lost to follow-up because of the linkages. This is an economical and high quality study that is accessible within a province or a hospital as part of the regular quality control for patient care. Using a database not only is economical, it ensures anonymity of both care providers and cases. This format for a study, using available resources, could be used for other purposes but is especially good within the cancer framework because of the existence of and the legislation surrounding cancer registries.

Table 7.1 Cross Tabulation of Marital Status with Age Category, Stage, Grade, and Group.

		Currently Married	Other
Age	<70	86 % 14 %	56 % 44 %
Staged	No	13 %	30 %
Graded	No	11%	15 %
Appointment	Yes	98 %	79 %
	No	2 5	21 %

Table 7.2 Cross Tabulations of Location with Age Category, Stage, Grade, and Group. n=1306

		Calgary	Edmonton	Southern Alberta	Central Alberta	Northern Alberta
Age	< 70	74 %	76 %	65 %	73 %	74 %
	≥ 70	26 %	24 %	35 %	27 %	26 %
Staged	No	14 %	17 %	29 %	31 %	16 %
Graded	No	20 %	7 %	15 %	10 %	5 %
Appointment	No	94 %	92 %	85 %	87 %	92 %
	Yes	6 %	8 %	15 %	13 %	8 %

Table 7.3 Cross Tabulation of Three Category Stage by Age Group, Marital Status, and Location for whole cohort, n=1389.

Stage		I & II (%)	III & IV (%)	Unknown (%)
Age Group	< 50	75	13	12
	50 - 69	76	10	14
	≥ 70	52	9	40
Marital Status	Currently Married	76	10	14
	Other	59	10	31
Location	Calgary	75	11	14
	Edmonton	73	9	18
	Southern Alberta	61	7	31
	Central Alberta	58	10	32
	Northern Alberta	67	15	18

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«LETTER_DATE»

Dr. «REF_DR_FIRSTNAME» «REF_DR_SURNAME»
«REF_DR_ADDRESS_1»
«REF_DR_ADDRESS_2»
«REF_DR_CITY», «REF_DR_PROV»
«REF_DR_POSTAL»

Dear Doctor «REF_DR_SURNAME»:

RE : «PAT_SURNAME», «PAT_FIRSTNAME»
Date of Birth : «BIRTHDATE»
ACB# : «ACB_NUMBER»
Site : «ICDO_SITE»

A report has been received that indicates the above patient has a known or suspected diagnosis of cancer. To register the patient with the Alberta Cancer Board, please complete Sections 1 and 2 of the attached Cancer Registration and Referral form. Please note, section 3 must be completed in order to indicate you wish the patient to be seen at the Cross Cancer Institute. If the patient does not have cancer, please indicate this on the form and return it to the Centre.

If you have any questions or concerns regarding the registration of patients, please contact Yvonne Williams or Sandi Schafer-Sherman at 432-8689 or by FAX at 432-8659. Your cooperation is appreciated.

Carol Russell
Manager
Cancer Registry
Division of Epidemiology, Prevention and Screening
CCI

per:
Lorraine Cormier, secretary



ALBERTA CANCER BOARD
CANCER REGISTRATION AND PATIENT REFERRAL

SECTION 1

PATIENT IDENTIFICATION

DATE:

SURNAME	GIVEN NAMES	MIDDLE
BIRTH DATE (YR/MO/DAY)	PHONE NO. ()	HM. () WK. ()
ADDRESS	CITY	PROV. POSTAL CODE
PHN	GENDER	OCCUPATION MOST OF LIFE
MARITAL STATUS	NAME OF SPOUSE	
BIRTHPLACE	SURNAME AT BIRTH	
HAS PATIENT HAD A PREVIOUS APPOINTMENT YES ☐ NO ☐ IF YES PLEASE SUPPLY CLINIC NUMBER		

SECTION 2

TO REGISTER MALIGNANT SITE - COMPLETE SECTIONS 1 and 2

SITE	HISTOLOGICAL TYPE	GRADE
STAGE	METHOD DIAGNOSIS: TISSUE ☐ X-RAY ☐ OTHER ☐ SPECIFY	DATE OF DIAGNOSIS HOSPITAL
IS PATIENT AWARE OF THE MALIGNANT DIAGNOSIS YES ☐ NO ☐ (SPECIFY)		
PRIOR MALIGNANT DIAGNOSIS	YES ☐ NO ☐	SITE: DATE: HOSPITAL:
THIS PATIENT WILL RECEIVE FOLLOW-UP CARE FROM:		
REGISTERING PHYSICIAN (please print)		DATE:

SECTION 3

TO REFER FOR AN APPOINTMENT - COMPLETE SECTIONS 1, 2 and 3

REFERRING PHYSICIAN	REFERRING HOSPITAL	UNIT	HOSPITAL NUMBER
TYPE OF SURGERY:	SURGEON	DATE	
DIAGNOSIS: (include cell type)			
For Breast patients include node status			

REASON FOR REFERRAL ☐ CONSULTATION AND OPINION ONLY ☐ OPINION AND TREATMENT ☐ RADIOTHERAPY ☐ CHEMOTHERAPY ☐ ROUTINE FOLLOW-UP ☐ COLPOSCOPY ☐ OTHER (PLEASE SPECIFY)

	TYPE	DATE	LOCATION	TYPE	DATE	LOCATION
PRIOR	☐ X-RAY			☐ U/S		
DIAGNOSTIC	☐ CT			☐ NUC MED		
TESTS	☐ MAMMOS			☐ OTHER		
	☐ MRI			☐ OTHER		

CHOICE OF CONSULTING PHYSICIAN(S)

COMMENTS:

SECTION 4

OFFICE USE ONLY:

	REQUESTED	RECEIVED	APPOINTMENT DATE AND TIME
SCANS X-RAYS			
PATH O.R.			
HOSPITAL D.S. OTHER			MADE BY: 186
SLIDE REVIEW			ON COMPUTER: _____

Appendix II - American Joint Committee on Cancer Staging Guidelines, 5th
Edition, 1997.

BREAST (continued)

Clin	Path	Stage Grouping			
[]	[]	0	Tis	N0	M0
[]	[]	I	T1*	N0	M0
[]	[]	IIA	T0	N1	M0
[]	[]		T1*	N1**	M0
[]	[]		T2	N0	M0
[]	[]	IIB	T2	N1	M0
[]	[]		T3	N0	M0
[]	[]	IIIA	T0	N2	M0
[]	[]		T1*	N2	M0
[]	[]		T2	N2	M0
[]	[]		T3	N1	M0
[]	[]		T3	N2	M0
[]	[]	IIIB	T4	Any N	M0
[]	[]		Any T	N3	M0
[]	[]	IV	Any T	Any N	M1

*T1 includes pT1mic.

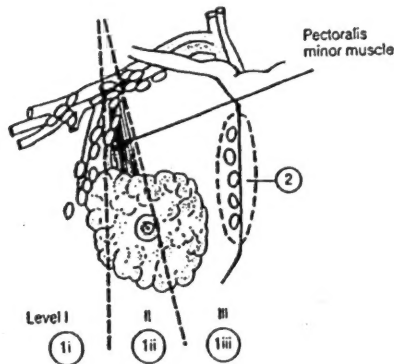
**The prognosis of patients with N1a is similar to that of patients with pN0.

Staged by _____ M.D.

Date _____ Registrar

Illustrations

REGIONAL LYMPH NODES



Histopathologic Grade (G)

- [] GX Grade cannot be assessed
- [] G1 Well differentiated
- [] G2 Moderately differentiated
- [] G3 Poorly differentiated
- [] G4 Undifferentiated

Histopathologic Type

The histologic types are the following:

Carcinoma, NOS (not otherwise specified)

Ductal

Intraductal (in situ)

Invasive with predominant intraductal component

Invasive, NOS (not otherwise specified)

Comedo

Inflammatory

Medullary with lymphocytic infiltrate

Mucinous (colloid)

Papillary

Scirrhous

Tubular

Other

Lobular

In situ

Invasive with predominant in situ component

Invasive

Nipple

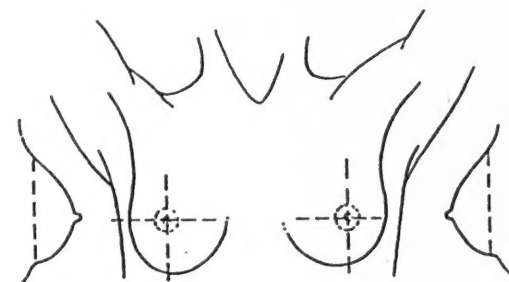
Page's disease, NOS (not otherwise specified)

Page's disease with intraductal carcinoma

Page's disease with invasive ductal carcinoma

Other

Undifferentiated carcinoma



Indicate on diagram primary tumor and regional nodes involved.